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FROM THE PREFACE

The present time has seemed to me fitting for the production of a text-book which while not neglecting the data of physiology, should lay special stress on the significance of these data, and attempt to weave them into a fabric representing the principles which are guiding physiologists and physicians of the present day in their endeavors to extend the bounds of the known and to increase their powers of control over the functions of living organisms.

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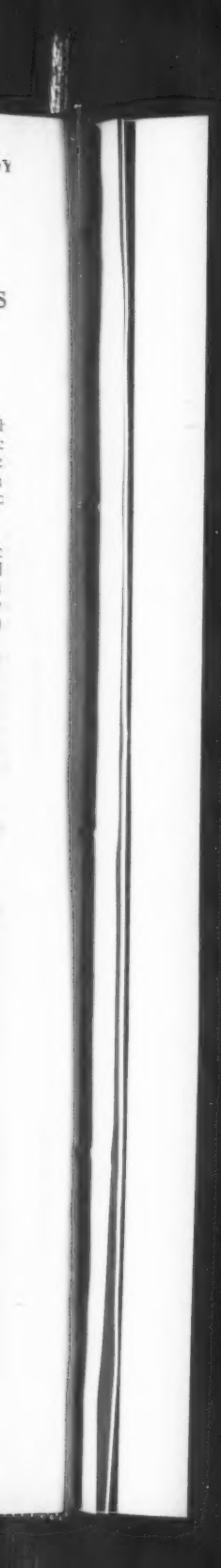

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THE

AMERICAN JOURNAL
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OCTOBER, 1912

ORIGINAL ARTICLES

DEFECTIVE DEVELOPMENT FROM ARTHRITIS IN EARLY LIFE.

By George Dock, M.D.,

PROFESSOR OF MEDICINE IN WASHINGTON UNIVERSITY, ST. LOUIS.

Chronic arthritis is rare in children, and this partly explains why many details are not as thoroughly known as is desirable. So, very few writers even mention the arrested development that might be expected from non-use or other causes in such cases. Osler quotes Still, who, in the first edition of Allbutt's *System*, volume iii, page 104, in describing the disease sometimes called after him, says: "In cases beginning before the second dentition there is often a marked arrest of bodily development; a child twelve and one-half years of age, in whom the disease began at four years of age, still had the appearance of a child six or seven."

Ollier first demonstrated that injury to epiphyseal cartilages causes retardation of long growth. Bidders and Vogt saw shortening after partial destruction of epiphyseal cartilages. J. Wolff showed that loss of growth in bones might occur far from seats of disease, that is, in the feet in coxitis. In contrast with these changes that seem not unexpected, Diamantberger and others have noted an enlargement of the great toes, which indicates a nutritional change of a less simple character.

I recently had a case under observation in which a youth aged twenty-four years, with a history of arthritis without heart lesion from the age of eleven, had slight general retardation as shown

by puerile figure and expression with defective development of the long bones and relative or absolute shortening of the bones of the extremities. I anticipated an opportunity for thorough Röntgenologic and other study of the bones and joints, but a terminal nephritis hastened the fatal end and an autopsy could not be obtained. It seems to me, however, that a report of the case may serve to direct attention to more thorough examinations in other cases, and that ultimately the processes involved may be explained.

Abstract of History. C. C.; single; aged twenty-four years; white; newsboy; admitted December 13, 1911, to Medical Clinic of Washington University Hospital; died January 7, 1912. No autopsy.

Abstract from St. Louis Children's Hospital records: First admission, September 22, 1900. "Two years ago patient had grip, which resulted in rheumatism." Physical examination shows greatly enlarged and painful joints, especially the small joints. Diagnosis: Arthritis deformans, chronic.

Second admission, October 1, 1901. Aged thirteen years. Diagnosis: Arthritis deformans. April 20, 1902, discharged; improved.

Present complaint "rheumatism."

Family History: Mother is living and well; aged forty years. Father died of rheumatism at thirty-one. Had three brothers and one sister, all in good health. One brother had an attack of rheumatism six years ago, but recovered completely.

Personal History: Never was sick until he was eleven years old. "Rheumatism in ankles from wet feet and exposure" was first trouble. Had diphtheria, measles, and scarlet fever at Children's Hospital when about fourteen years old. Had mumps and whooping cough at about the same time. Had measles last and seemed to be in much better health afterward than he had been before. "Rheumatism" has been constant, but was less severe after measles. Was out of Children's Hospital for a year and a half, then went to St. Luke's Hospital; was there nine months, and was much improved. Could get along very well with a cane when he left. Was not troubled much about walking for one year, then ankle was sprained and use of crutches begun. Has not been able to discard them since. Had gonorrhea four years ago; recovered in six weeks. Joints not affected at that time. He had occasional headache; nose has been partially obstructed since childhood. No pneumonia or bronchitis; no dyspnea; no pains in chest. No precordial pains or palpitation. Heart has never been said to be affected. Has had "indigestion" since two months ago. Patient thinks trouble is due to bad teeth; is sure it did not come from food. If too much liquid is taken vomiting occurs immediately after eating. Sometimes vomiting

does not occur for an hour, and sometimes in the morning previous supper is vomited. Vomitus always consists only of food taken at previous meal; often is bile-stained, but never has been stained with blood. If vomiting occurs several hours after eating the vomitus is scanty, a severe headache is always associated with vomiting. Headache stops in an hour after vomiting. Has no pain in stomach. Passes urine four to six times each night and once or twice during the day. No pain on urination. Large amount of urine of high color voided at night, but no great amount at one time. Urination is urgent and involuntary if closet is not reached at once. Muscles are very weak. Mental and nervous condition fairly good.

Uses small amount of coffee and tea, also small amount of beer and whisky; two or three drinks each week. Sleeps well, eats well. Has worked as newsboy on the street for several years.

Present disease, patient says, began in ankles after exposure and wet feet about thirteen years ago, when aged eleven years. Ankles were swollen and stiff for a week or two, then swelling moved up the muscles of both legs to the knees, which became swollen, hot, and red. Swelling spread upward until shoulders and arms were involved. Nearly all of the joints are stiff and the muscles are very small and weak. There is no continuous pain, but pains shoot from one joint to another. No pain in muscles. Throat and neck swollen for about two months. Never has been painful.

Present condition. December 13, 1911. Patient is a sparely nourished young adult. Gums and mucous membranes pale. Pupils equal; react to light and accommodation. Ears and nose free of discharge. Marked swelling of tissue about neck and side of jaws, the normal lines being partially obliterated. No tenderness, nor can any glandular structures be palpated. No fluctuation.

Tongue coated, breath foul. Teeth in poor condition—pyorrhea alveolaris; no general glandular enlargement; nasal obstruction.

Thorax long, costal angle narrow, expansion slight; better over right front. Percussion note clear in front and in axillæ, auscultation negative. Heart: maximum impulse in fourth interspace, just inside the nipple line, 7.5 cm. from midsternal line. Heart action regular; sounds clear all over; slight accentuation of second pulmonic. Radial pulse regular, 84 to minute.

Abdomen natural looking; moves well; no masses or tenderness. Liver dulness begins above at bottom of fifth rib and ends one finger-breath below costal margin. Edge just palpable. Genitalia normal. Spleen not palpable.

Extremities. Marked atrophy in upper and lower extremities. There is fixation of right elbow and right wrist; marked thickening of middle phlangeal joints of both hands. On left, there is good motion in left elbow joint. There is ankylosis of both hip joints and partial ankylosis of both knee and ankle joints.

Blood, December 14, 1911: Red corpuscles, 5,200,000; leukocytes, 11,000; hemoglobin, 70; color index, 0.7.

Urine examination, December 12, 1911. Specific gravity, 1009; acid; cloudy; albumin, large amount; 1 per cent. by Esbach; sediment contains many hyaline, waxy, and cellular casts.

FIG. 1.—Photograph of patient showing his youthful appearance, the atrophy of the extremities, and the extent of the arthritis.

Note by Dr. Dock, December 15, 1911. Patient has an unusually youthful appearance; the arms and legs are poorly developed, the arms are very short (see measurements). The frame is juvenile, but the body hair and external genitals are well developed.

The appearance of the patient is best appreciated from the photograph, but a few of the measurements are given (*a*), with the measurements of a normal individual of about the same height

(*b*) and those from another case (*c*) of chronic arhtritis, beginning at nine years of age with more marked fixation than the patient, but without special developmental defect.

FIG. 2.—Röntgenograph showing the changes in the bones and joints.

	A. cm.	B. cm.	C. cm.
Vertex to perineum	84.0	98	75.0
Vertex to navel	64.0	..	58.0
Clavicles	12.0	..	12.5
Shoulder to elbow	27.0	31	30.0
Elbow to wrist	18.0	25	18.0
Wrist to end of middle finger	16.25	18	18.0
Crest of ilium to trochanter	15.0	15	13.0
Trochanter to knee	36.5	40	35.0
Knee to external malleolus	35.5	41	34.0
External malleolus to sole	6.5	7	4.0
Length of foot	19.0	27	21.6

The excretion of urine became smaller, the stomach became so intolerant of food that enemata were used, and they, too, soon became impossible to retain. Later the patient became comatose, and died next day, January 6, 1912.

The changes in the bones and joints can be realized fairly well from one of the many röntgenographs made by my colleague, Dr. R. D. Carman. The bones show rarefaction as is common in cases of chronic arthritis. Besides the erosion, cupping, and exostosis of the articulating ends, there is the not uncommon change in the shape of the heads of the bones, so that the heads of the humerus and femur, and the condyles of the femur and head of the tibia seem elongated. The shafts of the long bones are unusually thin and slender and the metacarpal bones and phalanges have cupping and broadening of the articular surfaces and narrowing of the shafts, somewhat suggestive of achondroplasia. It seems to me impossible to exclude the latter process, but I present the case without further comment.

THE METABOLISM AND SUCCESSFUL TREATMENT OF CHRONIC JOINT DISEASE: A PRELIMINARY REPORT.

By Ralph Pemberton, M.S., M.D.,

PHYSICIAN TO THE OUT-PATIENT DEPARTMENT, PRESBYTERIAN HOSPITAL; FELLOW OF COLLEGE OF PHYSICIANS, ETC., PHILADELPHIA.

(From the Department of Clinical Chemistry, Presbyterian Hospital, Philadelphia.)

It is a familiar clinical fact that chronic joint troubles form one of the most frequent and rebellious of diseases. The application of laboratory methods to the diagnosis of the several varieties and the rational treatment dependent upon it have reduced many of these to categories which are fairly well understood and yield good results. Thus the tuberculous, Neisserian, and specific joints tell their own story, but after eliminating them there remains a large class in which but little progress has been made. This is the class grouped by various writers under the headings, rheumatoid arthritis, chronic articular rheumatism, arthritis deformans, and so on, conditions having in common an obscure or doubtful etiology and a prognosis for the most part unfavorable.

The activities of certain workers, particularly perhaps Goldthwaite and his collaborators in this field, have brought some order out of chaos, but it should be noted in passing, and with no credit to the internists and laboratory men, that it remained for orthopedists to suggest the simplest classifications and to practise the most rational therapy. It is due chiefly to the above men, for example, that we recognize in these obstinate cases the importance of a focus of infection in a tooth or tonsil, and that regulation of the diet along broad and intelligent lines is of the utmost value

in the undernourished and overfed. And again, we are now aware of the toxic possibilities incidental to a ptosed colon for which abdominal supports and operation have given much relief.

Grouping these cases as a whole, however, and eliminating them in turn from consideration, there remains a large and distressing number of cases which progress from bad to worse despite surgery, good hygiene, overfeeding, and underfeeding.

The principles of treatment as outlined above are now generally observed and practised by careful clinicians, but that they often fail is common knowledge. That the intestinal tract, however, is in some way or other connected with most of these last toxic arthritides is becoming more and more the belief of those who most frequently handle such conditions, but after what fashion it operates or what should be done for relief is not so clear.

In those instances where support for intestinal prolapse is not needed or fails, or where operation is not practicable or successful, there is often recourse to a consideration of diet, and it is partly with this phase of the subject that we wish now to concern ourselves.

More specific and detailed knowledge is obviously needed, and for lack of it, dietary control of these rebellious cases is practically renounced as impossible and not attempted.

The necessity of treating a number of sufferers from the conditions above indicated brought home to the author the desirability of some definite observations by clinical and laboratory methods from which an etiology and treatment could be deduced.

It is advised by many, for example, that in the dietary supervision incidental to good hygiene consideration should be had as to constipation, flatulence, the caloric need of the thin individual and the caloric surfeit of the fat individual, and that only the digestible foods should be eaten, that abundance of water should be ingested, and the like. At last analysis, however, these instructions are too generic, and in application generally fail of their purpose. Specifically stated, to feed these individuals with due regard to their nutritive needs and at the same time to avoid the element or elements which cause the joint disturbances, is the problem which presents.

Having found such a dietary regimen there would be offered thereby an opportunity for study of the processes active for good and evil which might yield facts of the utmost value. Why such a study has not been attempted before is not clear to the writer, since opportunity has at times presented in those cases which have yielded to the correction of intestinal ptoses.

Reference to the literature, however, indicates that while the contributions to chronic joint diseases have been legion, they have rarely been specifically along the lines indicated, and have rarely been accompanied by careful laboratory studies.

It has seemed evident for some time past to the writer that in

these joint conditions of intestinal origin several causative possibilities presented. (1) There is to be considered the activity of the intestinal flora *per se*, generally accepted for the most part as putrefactive, whose growth and by-products might cause absorbable toxic matter. (2) There is their action upon the ingested food to be considered, by virtue of which there may occur substances whose absorption might be causative of trouble. (3) There is the possibility of some defect in that disintegration and synthesis which gives rise to the "bau-steine," as a feature of pure physiological or pathological metabolism. How best to control the conditions of experiment to obtain a clue as to which possibility, if any, is operative, must be determined.

The writer has observed in a number of instances the remarkably beneficial effect of purgation and starvation upon the symptoms of certain joint cases, and the question is raised as to whether this be due to the absence of food decomposition and synthesis, to a diminution of intestinal bacterial activity, or to both. That the amount of food *per se* is an important factor apart from its relation to bacterial activity is indicated somewhat by the well-known favorable action of arsenic in these states, one action of which is probably to hasten the general metabolic processes. Another agent capable of this same action, though to a greater degree, is thyroid extract, whose gradual effect on nitrogenous exchange and the persistence of this after administration of the drug has ceased, are testified to by many observers.[1]

It is plain, therefore, that a great reduction of the food intake, active purgation, or the administration of agents which hasten the general body metabolism act beneficially on the symptoms of these conditions. The last mentioned agents, furthermore, are often beneficial even in conjunction with little or no reduction of the ingested food and may even stimulate the appetite to a greater consumption. If we apply the reasoning here suggested it would seem likely that there is a point at which one or all of the elements of food can be assimilated with satisfaction to the body needs and without detriment to any particular structure.

The lesson to be learned is in some respects like that taught by gout and diabetes, though the particular elements harmful in joint disease must yet be determined. An effort was made along these lines, beginning with the simplest of foods in order that the effect of their several component elements might more clearly be observed. Milk suggested itself at once, of course, as a basis for experimentation and our intention at first was to use whole milk. Experience with one case, however, in which "buttermilk" was successfully administered, seemed to urge further trial of it, and more systematic study of the results obtained. The question of the value, if any,

[1] Von Noorden, Metabolism and Practice of Medicine, iii, 991.

of introducing fermentative organisms into the intestinal tract by this means is still *sub judice*, though the observations of Herter and others have indicated the great importance of more work along this line.

There can be very little doubt, however, of the importance of learning the effects in these cases of reducing to a minimum the activity of the usual intestinal bacteria, and the simplest method of achieving this, in some part at least, has been shown to be by frequent movement of the bowels and by colonic lavage.

"Intestinal antisepsis" comes in here for very little consideration because of the discredit into which it has been brought by most observers and because drugs in any event introduce complicating factors. Whether, in this connection, by feeding fermentative organisms in large quantities in the form of buttermilk there can be produced an actual replacement of the customary intestinal flora is a problem whose terms and possibilities are not yet clear. It is worthy of study, however, and offers at least an hypothesis for development.

We desire here to report, therefore, (1) the results of treatment by these means in a series of chronic joint cases, and (2) the results of metabolic study of some of these individuals at certain periods of their progress. This report is to be interpreted, however, as purely preliminary and subject to the results of further study along the same lines. This is now in process, and only because of certain extraneous factors is it deemed advisable to report the results to date.

CASE I.—Mrs. M., aged sixty years, in comfortable circumstances and the mother of three healthy grown children, had been accustomed to robust health and rather unusual physical activity. She was first seen January 19, 1911, complaining of "rheumatism" or "gout" in her fingers and knee.

Physical examination revealed swelling and pain of all but the terminal finger joints of both hands, which had been growing progressively worse since the previous August. The second phalangeal joints had suffered the most, compelling her to remove her rings, though the dorsum of the hands was also puffy. Active and passive motion of these joints caused pain, and some of them had limitation of motion. The left knee was also tender on certain forcible palpation and gave considerable pain on walking, causing a limp and curtailing activity. The patient felt somewhat depressed but had no other subjective symptoms. She was rather heavily built, had a chronically slightly coated tongue (a feature common to at least two of her children), and a well audible mitral systolic murmur, together with a slight systolic murmur at the aortic cartilage. There was no noteworthy enlargement of the heart, and there had never been loss of compensation. The abdomen was rather large, flabby, and fat, with thin muscular walls, and in the

erect posture was somewhat pendulous. The patient objected to having an *x*-ray picture taken to ascertain the exact position of the stomach and large bowel, but the evidence was all in favor of some ptosis of both organs.

Her bowels had always been freely open at least twice daily, and often moved three times. Her blood pressure was 175 systolic and 75 diastolic, by auscultation. The blood and urine were negative, and a careful examination of the ears, nose, and throat by Dr. George Stout revealed no focus of infection. The accompanying picture (Fig. 1) shows the bony changes in the finger joints, characteristic of well-marked atrophic and hypertrophic arthritis. The patient had always had a good appetite and had eaten generously of everything, though not to excess, and was not in the habit of using alcohol in any form.

On January 27 she was instructed to eat meat but once a day, to stop her tea and coffee, to drink four glasses of water in addition to the fluid at meals, and was given daily four glasses of buttermilk prepared by artificial lactic acid fermentation.[2] Her usual diet was reduced over a period of about a week until the daily regimen was about as follows:

One glass of water on rising. Breakfast, consisting of a small amount of cereal, with cream and sugar, and one or two slices of well-done toast, with butter, hot drink (imitation cereal coffee, any of several varieties on the market) with cream and sugar if desired.

Between breakfast and lunch: Two glasses of "buttermilk" and one glass of water.

Lunch: Clear soup (or lettuce or spinach), one roast potato, toast (two slices), imitation coffee.

Between lunch and dinner: One glass of "buttermilk" and one glass of water.

Dinner: Clear soup (or twice a week a small amount of roast chicken, or twice a week 1 egg), toast or lettuce, imitation coffee, apple sauce.

Between dinner and bedtime: One glass of "buttermilk" and one glass of water.

Every afternoon about 5 P.M. the patient was given a simple enema and then high colonic lavage, with about 1½ quarts of normal salt solution, the washings being repeated until they came

[2] The milk used was that marketed by the Supplee milk establishment under the trade name "Fermillac." Its approximate composition is given by the manufacturer as 3.6 per cent. fat, 5 per cent. sugar, 3.2. per cent. proteid, 0.8 per cent. lactic acid. It is a fairly constant product, free from lumps, and for the most part of uniform consistency, though at times, probably from unduly prolonged fermentation, it is somewhat "coppery" and disagreeably acid. Patients were told to avoid it under these circumstances. They all professed to like milk prepared this way and seemed not to tire of it. There are several equally desirable artificially soured milk products on the Philadelphia market. They differ from buttermilk in that the fat is not removed.

FIG. 1.—*X*-ray of hands of Case I, showing degree of joint involvement.

away fairly clear. Her bowels moved naturally in the morning. Later she preferred the injection in the morning about 10 o'clock, and was then given a glycerin suppository at bedtime, always with result. The injections were given daily from January 30 to April 24, on alternate days from April 24 to May 6, thence every third day for two weeks, and then discontinued. Great care was exercised, of course, to avoid the slightest pain or local irritation in their administration.

The progress of her case is interesting and as follows, from notes taken at the time:

January 26. Treatment started. Weight, 167½ pounds.

February 2. Feels distinctly brighter and fingers are smaller.

February 8. Much better.

February 10. Weight, 163½ pounds. Pain in knee less.

February 14. Weight, 163½ pounds. Fingers are less swollen than at any time yet. A ring which could previously be removed with great difficulty or not at all now comes off with relative ease.

February 25. Weight, 164½ pounds. Condition good.

March 16. Weight, 162½. Blood pressure: 156 systolic, 75 diastolic, ausculatory. Before instituting treatment it was 175 systolic, and 75 diastolic.

April 29. Weight, 162. Blood pressure: 158 systolic, 85 diastolic. Practically free from subjective and objective symptoms.

Further notes on this point are unnecessary as her condition was excellent and remained so all summer, despite the fact that for two months she lived at hotels and allowed herself much liberty in her diet. For one month she stopped the buttermilk entirely, retaining, however, her increased fluid intake and eating with moderation of meats and starches. About four months later, however, she appeared again for treatment.

As the result of the excitement of Christmas and the visits of some friends, as well, perhaps, because of deliberate intent, she began to eat more freely of puddings, rice pudding especially, and the so-called "simple desserts." On January 28 she weighed 157 pounds 3 ounces, and presented distinct pain and swelling in the ring finger of the left hand. She had of her own accord renewed the "buttermilk" in October, and was taking in January four glasses daily. She was then advised to stop all meat and starches except zweibach, to increase the milk by two glasses daily, and to rest more. She developed three days later bronchitis, with slight fever, cough, and coryza, but at the same time her fingers improved.

On February 15 she was given a squab for lunch, and from then on her diet was increased until at the end of March it averaged as follows:

Breakfast: Cereal with cream and sugar, toast, imitation coffee, with cream and sugar.

Lunch: Spinach, toast, "coffee."

Dinner: Roast chicken, roast potato, toast, "demi-tasse" of "coffee."

In addition to the above she had her usual amount of "buttermilk," four glasses daily, as above described.

The patient was perfectly content with this diet. By this time she felt well and was free from all joint manifestations. A short but sharp diarrhea during the attack of bronchitis had pulled down her weight, which recovered somewhat, and stood on March 25 at 151½ pounds. By April 18, however, she expressed herself as having never felt better, weighed 154¼ pounds, and was taking a practically unrestricted diet of everything that came to table, with the exception of obviously indigestible articles like corn and griddle cakes; the "buttermilk" had been reduced to four glasses daily. This served to lessen her appetite at table and reduced consequently the amount which she would otherwise have eaten. Though previously a large eater of meat she was now satisfied with smaller amounts. It is interesting to note that at the time of her relapse she had increased her usual dietary by starches and sugars only, and had taken no more animal proteid of any kind. Upon reducing these again and with her return to health her tongue changed its charter from being quite heavily furred and white to a nearly clear red. This excited her comment and was unique with her except for the periods of convalescence above mentioned.

Experience with this case determined the writer to pursue the subject in other individuals, more carefully and with laboratory methods.

The following represents the first attempt to that end.

Case II.—John H,. aged fifty-six years, a carpenter by trade, had suffered for five years past with increasing involvement of most of the fingers of both hands, both knees, especially the right, and the left foot. He also complained of stiffness and pain in his shoulders. His previous medical history was negative except for an attack of what resembled malaria and for the loss of one eye by accident eighteen years before. He had always been a great sufferer from constipation, and on occasion his bowels would not move for eight days. He denied alcoholic and venereal history, and was the father of several healthy children.

Examinations showed a spare man of middle height. Thorax and abdomen essentially negative, except for a palpable right kidney. Both hands showed extensive involvement, with marked deformity of the two middle fingers of the left hand. These were subluxated at the first phalangeal joint and presented distinct effusion.

The left knee was somewhat swollen, but the right foot was the part worst affected. It was swollen on the dorsal surface and pitted on pressure. There was no deformity of the toes, but pressure

below and anterior to the external malleolus, in fact most anywhere, gave much pain.

His weight was 115 pounds; blood pressure, 105 systolic and 52 diastolic. His blood count averaged: Red blood corpuscles, 3,130,000; leukocytes, 13,500 to 7000; hemoglobin, 70 per cent. An *x*-ray taken by means of bismuth showed that the stomach and colon were in the normal position and gave no clue as to the cause of his constipation.

This was deemed a good case in which not only to try the therapeutic effect of the diet described above, but also to attempt metabolic study, etc., of his condition before and after improvement, should this occur. To this end he was placed upon the following average diet:

December 27, 1911. Breakfast: Bread, 60 grams; two eggs, 89 grams; butter, 23 grams; milk, 256 c.c.; water, two glasses.

Dinner: Bread, 60 grams; rice, 41 grams; apple sauce, 127 grams; butter, 18 grams; milk, 256 c.c.; water, 1 glass.

Supper: Bread, 55 grams; two eggs, 90 grams; butter, 17.5 grams; milk, 256 c.c.

This diet varied slightly on different days according to the size and weight of the eggs, etc., but the amounts taken on the various days are omitted to save space. The sum total of ingested food appears in the accompanying tables.

Metabolic observations were conducted for four days on the following: Nitrogen of the urine, ammonia of the urine, creatinin of the urine, nitrogen of the feces, total sulphates of the urine, preformed sulphates of the urine, ethereal sulphates of the urine, total number of bacteria in the feces.

The methods employed were as follows: Nitrogen, Kjeldahl method; ammonia, Folin's method; creatinin, Folin's method.

The sulphates were precipitated with $BaCl_2$ and calculated as SO_3.

The determination of the fecal bacteria was by counting, and will be discussed and described under Case III. The results of the latter in this case were unsatisfactory.

The figures obtained from the analysis in Case II were as follows:

	December 28	December 29	December 30	December 31
Nitrogen of urine	14.3942 grams	11.2 grams	8.624 grams	8.1984 grams
Ammonia of urine	.3745 grams	.1632 grams	.1904 grams	.3917 grams
Creatinin of urine	1.1984 grams	1.009 grams	1.0657 grams	.8872 grams
Ethereal sulphates	....	.1419 grams	.1579 grams	.3694 grams
Preformed sulphates	....	....	2.1249 grams	
Total sulphates	....	....	2.2828 grams	

Total nitrogen of the urine	42.4166 grams
Total nitrogen of the feces	2.6289 grams
Total nitrogen egested	45.0455 grams

Total food ingested: Bread, 756 grams; eggs, 726.5 grams; butter, 219.5 grams; milk, 2834 c.c.; rice, 152 grams; apple sauce, 559 grams.

Total nitrogen ingested, 42.5695 grams. *Negative* nitrogen balance, 2.4760 grams. Comment on these figures will be made later.

This patient on January 2, 1912, was put upon a diet of "buttermilk," eight glasses in twenty-four hours, together with one egg at breakfast, one green vegetable at lunch, apple sauce at supper time. Later he was given one bowl of hot strained clear soup at lunch, as he suffered much from the cold weather and cold dietary. Because of his undernutrition it was thought well to push his diet as much as possible, and he was given on January 18, a total of ten glasses of "buttermilk." An effort was made to keep him out of doors in a chair, but he complained so from cold that this was discontinued. He was also given daily in the morning a simple enema, followed by high colonic lavage, with about two quarts of warm normal salt solution. In the early evening he was given a glycerin suppository, which was, however, invariably ineffectual. The enema usually gave some result, generally slight, and his bowels could not be said to move with much satisfaction.

The following notes show such progress as he made:

January 9. The swollen finger-joint (with effusion) shows slight improvement; foot no worse. Patient discouraged. Has been on diet about a week.

January 11. Slightly better. Finger-joint is smaller, with less effusion.

January 15. Distinctly better today for the first time. Swelling in foot is less. Complains of some pain in leg muscles.

January 16. Improves.

January 18. Still better. Right knee slightly swollen, probably from increased activity. Swelling of right leg below the knee has now practically all gone; took ten glasses of "buttermilk" in all today.

January 19. Both foot and knee better. Weight, 112½ pounds. Swelling of foot practically gone.

January 28. Slight swelling of foot today. Nails very blue after being out in the cold air. Two more glasses of "buttermilk" to be given daily.

January 30. Foot still swollen in afternoon and somewhat so at other times of day, but much less painful—in fact, almost free from pain.

From this date on there was very little appreciable change in the man's condition. The swelling of his finger had subsided not to return, his general health was better, the pain in his foot was so diminished that he could at times walk with relative ease, but the

edema of this one foot persisted, and he complained of pain in his shoulders, which kept him awake at night.

It had been the hope of the writer that at about this date or later another period of metabolic study could be undertaken, with the idea of comparing the various findings during improvement with those of the first period. The patient's condition, however, did not warrant the attempt, as he had not sufficiently improved. After a few weeks spent in the hospital he became restless, and was discharged at his own request.

In retrospect several errors can be detected in the attempt made with this case. The patient's general health had been so undermined, his constipation was of such an obstinate and long-standing nature, and he had such a marked anemia that a mistake was made in putting to the test with him any therapy without first relieving or modifying these conditions.

It was not desirable to cloud the issue by the simultaneous exhibition of iron, aresnic, etc., especially since metabolic observations were contemplated; but his anemia should have been actively treated, his constipation combated, and his weight increased if possible before the therapeutic test of his joint condition by means of dietary measures.

It is but just to say, furthermore, that this patient had been through half a dozen "cures" in this country and had tried many other treatments without avail. By the time that the arrest in his improvement became clearly evident, he grew restless, as mentioned, and desired to leave the hospital.

Furthermore, he required a degree of personal care in the way of massage and alcohol rubs to induce sleep, etc., which could hardly be administered with success in the public wards of a hospital, but he was of the opinion, judging by his own subjective experiences, that dietary regimen offered the only prospect of relief.

Case III.—The next case studied was of greater interest possibly and gave much more encouraging results. The patient was a woman, aged thirty-seven years, who was deliberately chosen by the writer and asked to submit herself to treatment because of two facts: (1) She presented an unusually typical case of atrophic arthritis, of nine years' standing, in a young woman without other disturbances of health. (2) She had tried nearly every known treatment in a long series of hospital readmissions, during which she had been under the observation and care of at least nine careful clinicians. It was felt that success and study in her case would be especially satisfactory because of both the well-marked and progressive nature of her condition and the clear failure of other means of treatment. The essentials of her history, etc., were as follows:

Mrs. F., aged thirty-seven years, white, presented a negative

family history and had always been healthy until the onset of the present trouble. She had one healthy child, aged twelve years. In December, 1903, she was operated upon at the German Hospital, Philadelphia, for appendicitis by Dr. John B. Deaver, and made an uneventful recovery, except for long-continued drainage of the abdomen. Three months later, after returning to her duties, she noticed an ephemeral and shifting stiffness of various joints accompanied by transient swelling. One year later this had resulted in a chronic swelling and disability of the middle finger of her left hand. From this time she progressed steadily from bad to worse. Because of the arthritis she was admitted three times to the Hospital of the University of Pennsylvania for periods of six months, five weeks, and four months respectively, and while there had her tonsils removed and a rectocele repaired. She was also treated for a temporary cystitis of origin subsequent to her joint trouble. She was also admitted three times to St. Timothy's Hospital, Roxborough, for periods of three days, seven weeks, and two weeks respectively, where she had some further remaining tonsillar tissue removed. Apart from this she had been under private professional care on many occasions.

Aspirin usually gave her relief from pain, but for a few hours only, and the one other measure of any avail was thyroid extract. This was administered during one of her periods at the University Hospital, with relief for some months, when she relapsed worse than ever. A second administration of the same drug at St. Timothy's Hospital was not only without benefit to her joints, but seemed to make them worse, and resulted in tachycardia and other symptoms of hyperthyroidism.

On the present admission she presented swelling, subluxation, hyperextension, atrophy, pain, limitation of flexion, and ulnar deviation of the fingers of both hands. There was also marked involvement of the elbows and of both knees, especially the right, which was swollen and partially ankylosed in slight flexion. The left ankle also presented marked swelling and pain below and external to the external malleolus, which was hidden by the tumefaction. She could barely use her hands to write, and she could not bear her full weight on either knee or ankle, much less walk. She was confined to bed and required assistance in caring for herself even in bed.

Her physical examination was negative in other respects, except for considerable corpulence, chiefly of the past year's duration, a large relaxed abdomen, and the fact that an *x*-ray photograph by Dr. W. S. Newcomet showed marked ptosis of the transverse colon, with sharp angles at the hepatic and splenic flexures.

The *x*-ray photographs of her hands showed a well-marked atrophic arthritis, with relatively little deformity, but marked rarefaction of the heads of the bones and almost total absence of

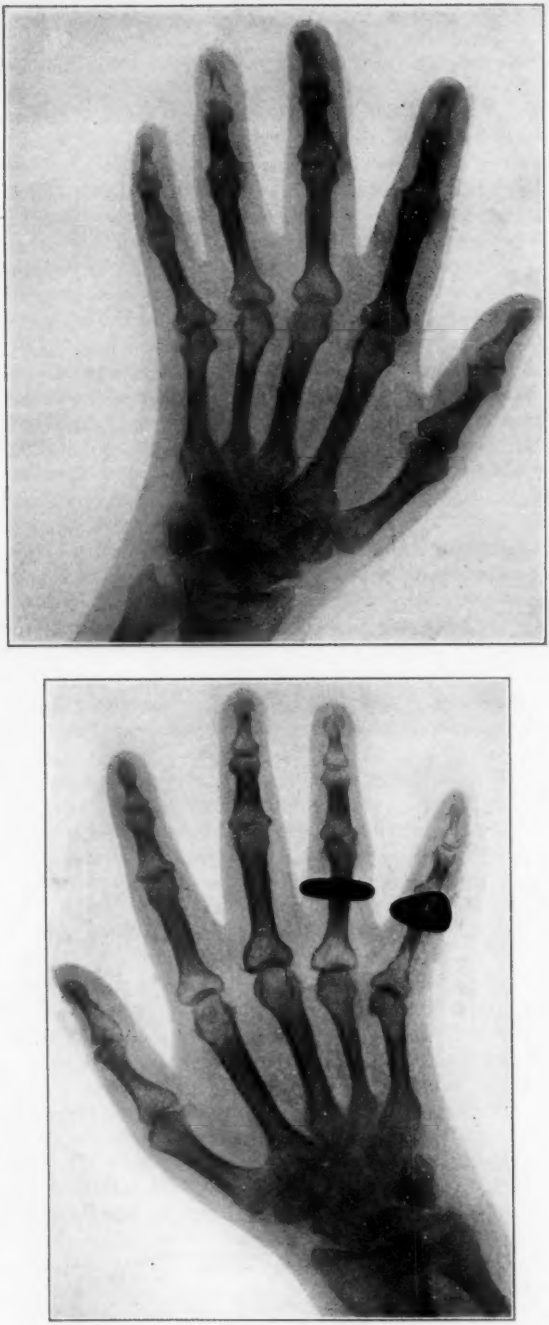

FIG. 2.—*X*-ray of hands of Case III, showing degree of joint involvement. The reproduction imperfectly illustrates the atrophic nature of the arthritis.

intra-articular cartilage. The plate of the right knee showed effusion and that of the foot some subluxation, in addition to the other characteristic phenomena of atrophic arthritis (Fig. 2).

The attempt was then made as with Case II, but here carried further, of placing the patient upon an average known diet, of no particular therapeutic value, in order to determine her metabolism while the diseased process was active. She was then placed upon the modified diet, and when improvement was sufficiently advanced another series of metabolic determinations was made. The results of these attempts follow.

On January 23, 1912, she was given the following average meals as the dietary of her first metabolic period and was kept in bed:

Breakfast: Bread, 47 grams; milk, 210 c.c.; one egg, 56.5 grams; water, 200 c.c.; butter, 13.5 grams.

Dinner: Bread, 27 grams; butter, 13.5 grams; milk, 300 c.c.; rice, 42 grams; sugar, 13 grams.

Supper: Bread, 42.5 grams; milk, 220 c.c.; one egg, 44.5 grams; water, 220 c.c.; butter, 13.5 grams.

The exact quantity of ingested food is tabulated later.

After she had been on this diet for three days her metabolism was studied with respect to the following: Nitrogen of the urine, ammonia of the urine, creatinin of the urine, ethereal sulphates of the urine, preformed sulphates of the urine, total sulphates of the urine, nitrogen of the feces, total number of fecal bacteria.

The figures follow:

	January 27	January 28	January 29	January 30
Quantity of urine	1016 c.c.	1030 c.c.	940 c.c.	760 c.c.
Nitrogen of the urine	9.5756 grams	7.4466 grams	8.5660 grams	10.1360 grams
Ammonia of the urine	.3713 grams	.2570 grams	.2856 grams	.3536 grams
Creatinin of urine	.9804 grams	.7896 grams	.9490 grams	1.0830 grams
Ethereal sulphates of urine	.3673 grams	.3865 grams	.3557 grams	.4124 grams
Preformed sulphates of urine	....	2.0262 grams	3.1260 grams	2.1913 grams
Total sulphates of urine	....	2.4127 grams	3.4817 grams	2.6037 grams

Total nitrogen of the urine	35.7242 grams
Total nitrogen of the feces	1.1718 grams
Total nitrogen egested	36.8960 grams

Total number of bacteria eliminated in four days by bowel, 373,750,000,000.

The total food ingested was as follows: Bread, 469 grams; butter, 160 grams; eggs, 405 grams; milk, 3530 c.c., rice, 108.4 grams; sugar, 52.5 grams; which yielded 36.266 grams nitrogen ingested. Negative nitrogen balance, 0.530 grams nitrogen. Her weight remained about 163 pounds.

On the completion of the above observations she was placed upon the following regimen:

Breakfast: Two glasses "buttermilk," one slice of toast and butter.

10.00 A.M. Enema of salt solution followed by colonic irrigation.

11.00 A.M. One glass "buttermilk."

12.30 P.M. Lunch of one glass "buttermilk," one green vegetable (spinach, lettuce, onions, cabbage).

3.00 P.M. One glass of "buttermilk."

5.00 P.M. Supper: Two glasses of "buttermilk," one slice toast and butter, one saucer apple sauce or stewed pears (not very sweet).

8.00 P.M. One glass of "buttermilk."

Water *ad libitum*, but she took very little.

The notes of her condition follow:

February 1. Diet started.

February 5. No indican, which had previously been abundant. Has a slight cold. No acetone. This was watched because of the reduction in the carbohydrates.

February 8. Hands seem much better. Gain of one-half pound in weight—now 159 pounds. Patient shows an unmistakable change since her new diet. Urine somewhat cloudy and shows white blood cells.

February 9. Hands slightly more tender in a few finger-joints, but no more swelling. No indican.

February 10. Doing well. Swelling of dorsum and of metacarpophalangeal articulations decreasing daily. Dimples begin to show over joint sites. Lost one pound.

February 12. Doing well.

February 13. Better. She is usually worse for one week prior to her menstrual period, but has escaped this time, though it is due tomorrow. This is her first experience of this. She says she moves better in bed and does not waken so stiff. Considerable indican today, probably referable to her period.

February 14. Menstruating. Slight soreness of hands. Possibly slight "cold" also.

February 22. No indican. Doing well.

February 27. Doing well and nearly free from pain on pressure over most joints or on motion of them. A ring which could not previously be removed without soap and water and much effort came off with relative ease for the first time.

February 28. Now getting the following average diet:

6.00 A.M. One glass of "buttermilk."

Breakfast: One glass of "buttermilk;" toast, 26 grams; butter, 6 grams;

10.00 A.M. One glass of "buttermilk."

12.00 N. Dinner: Lettuce and salt, 24 grams; one glass of "buttermilk."

2.00 P.M. One glass of "buttermilk."

4.00 P.M. One glass of "buttermilk."

6.00 P.M. Supper: Apple sauce, 172 grams; toast, 24 grams; butter, 5 grams.

8.00 P.M. One glass of "buttermilk."

9.00 P.M. One glass of "buttermilk."

Daily enema and colonic lavage still being administered. Weight, 159 pounds.

The patient had by now progressed so far that the second period of metabolic study seemed advisable.

Her diet was therefore carefully weighed and measured, the results of which in terms of total ingested food for the period follow.

The figures obtained from a four days' metabolic study while she was still in bed are:

	February 29	March 1	March 2	March 3
Quantity of urine	1930 c.c.	1650 c.c.	2130 c.c.	1350 c.c.
Nitrogen of urine	7.7280 grams	7.2990 grams	8.2544 grams	6.5856 grams
Ammonia of urine	.4896 grams	.3590 grams	.4488 grams	.3808 grams
Creatinin of urine	.8728 grams	.8969 grams	.9548 grams	.7042 grams
Ethereal sulphates of urine	.4884 grams	.4302 grams	.5251 grams	.3390 grams
Preformed sulphates of urine	2.0558 grams	2.1611 grams	2.0795 grams	1.4565 grams
Total sulphates of urine	2.5442 grams	2.5913 grams	2.6047 grams	1.7955 grams

Total nitrogen of the urine	29.8670 grams
Total nitrogen of the feces	2.8684 grams
Total nitrogen egested	32.7354 grams

Total number of fecal bacteria eliminated in four days, 12,372,000,000,000.

Total food ingested: Toast, 201 grams; butter, 46 grams; "buttermilk" or "Fermillac," 8192 c.c.; lettuce, 150.25 grams; apple sauce, 607 grams; apples, 438 grams; which yielded *in toto* 41.3554 grams nitrogen.

There was therefore a *positive* nitrogen balance of 8.62 grams.

Subsequent notes are as follows:

March 4. Slight "cold" possibly. No fever. Right hand and wrist slightly sore. Allowed up. Weight, 159 pounds. Out in chair on piazza. Out every day on piazza. Her ankle is now much less painful, as is also her right knee. Wants to get up and go home.

March 29. Slight pains today in one hand and right elbow, due to approaching menstruation, possibly, which sometimes comes slightly ahead.

March 31. Menstruating. Diet increased to a total of one egg and fruit at breakfast, one slice of toast at each meal, one vegetable and soup at lunch, two green vegetables and stewed fruit at supper, with usual amount of "buttermilk."

April 4. Taking increased diet well and is apparently cured of

all active processes in her hands. The only painful parts are in the right knee, where the disability is possibly mechanical, and to a slight extent in the malleolus. This may also be mechanical, as the *x*-rays show a subluxation in the foot. Weight, 157 pounds.

April 26. Diet has been increased and the "buttermilk" reduced to only five glasses daily. Now taking chicken and a roast potato at lunch in addition to the egg at breakfast and green vegetables at supper; also has ice cream at times. Took fish from another patient once without orders, but it did not hurt her. Has had massage and stretching of her slightly contractured right leg, which is now becoming straighter. Is up and around the ward a little every day, and says that her foot is nearly or entirely free from pain. Menstruating today, but has no exacerbation of any symptoms, as occurred prior to treatment.

Enough has been said of the course of this case to show that to all intents and purposes her inflammatory arthritis at this point had subsided. In conjunction with the case first cited and the previous history of the present case the results leave no room for doubt as to the importance of these measures in at least some instances.

Metabolic Findings. The metabolic figures of Case II are given for what they are worth, but since no control observations could be made during marked improvement their value is minimized. They show nothing that could not be encountered in health, though the ethereal sulphates are conspicuously low as compared with the next case, and, indeed, are low for any individual who suffers much from constipation.

Metabolic observations on such cases during the activity of disease are not lacking, but data on the relative proportions of the various factors then and during convalescence are rare.

Turning now to Case III a review of the figures is more profitable. In the first metabolic period we find an output of ammonia which is just about in accord with what is usual in health, though verging on an output actually low.

The creatinin is about normal, as it also was in Period II, and can be dismissed from further notice. It is evident, so far as the creatinin output can be taken as an index of general muscular metabolism, that internal muscular metabolism *per se* plays no important role in this condition.

Considering next the ethereal sulphates we find rather high values, which might be expected *a priori* perhaps, though they are not excessive. It is interesting to note in connection with the ethereal sulphates here and in the next period that "Keffir"[3] has been mentioned in doses from 1 to 1.5 liters a day as an excellent remedy with which to combat intestinal putrefaction.

[3] Simon, Clinical Diagnosis, fifth ed., 408.

Comparing then the ethereal sulphates of Period I with those of Period II, there is found a surprising rise in the latter, when the patient was improving rapidly, associated with a decrease or absence of indican.

Whereas they had averaged in Period I about 0.3805 they rose in Period II to 0.4457, an increase of 17 per cent. The ratio of conjugate to preformed sulphates in the first period was 1 to 6.4; in the latter period it rose to 1 to 4.3 in spite of ample daily bowel movements and lavage of the colon.

The amount of nitrogen ingested was smaller and the amount of nitrogen egested was larger in Period I than in Period II.

It is hard to explain how the introduction of large amounts of lactic acid organisms can in any way have contributed to this increase of the ethereal sulphates, since they are supposed, as above cited, to lessen intestinal putrefaction.

The positive nitrogen balance, however, shows that the patient handled with success a larger amount of proteid in her second period, and this may have explained, notwithstanding the decreased nitrogen output, the increase noted.

If the conjugate sulphates be a true criterion of the so-called intestinal putrefaction, we must deduce that, in this case at least, intestinal putrefaction was not a serious etiological factor and the cause of disease must be sought elsewhere than in the putrefaction of proteids. As a matter of fact, the writer has been inclining to the view, to which this lends color, that an important noxious role is played here perhaps by the carbohydrates, particularly the starches. Other clinical evidence indicates much the same, and it can be shown in some of these patients that entire curtailment of proteid other than milk will not help them if they be fed generously with carbohydrates. In fact, as just shown, the proteid intake was actually increased in this present case, before and during the improvement. One case does not warrant postulates on this score, but it is at least suggestive.

It is interesting to note that in the patients who improved a great change appeared in their stools. For example, whereas Case I had had for perhaps forty years from two to five stools daily, of a frothy, loose nature, these became transformed after her new dietary into more mushy, semiformed or formed stools passed but once a day, unless a suppository was resorted to later. We have had the same experience in certain other cases where the carbohydrates were reduced, and there can be but little doubt that these were responsible for the change. There seems to be in this further suggestive association of the carbohydrates with conditions of the disease.

The ammonia in both metabolic periods of Case III was within reasonable limits, though it showed a rise from 3.4 per cent. of the urinary nitrogen in Period I to 5.6 per cent. of the urinary nitrogen

in Period II. This can hardly be interpreted as implying more than would be expected in view of the considerable quantities of lactic acid consumed.

The preformed and total sulphates showed no marked change in the two periods, were of average amount, and interesting chiefly because of their relation to the conjugate sulphates.

We now approach the interesting though difficult question of the fecal bacteria. What role these play in normal physiology is by no means clear, to say nothing of their relation to diseased processes, but increasing investigations point to the desirability of further knowledge along this line, despite the technical difficulties presented. We are well aware of the skepticism with which this field is regarded, and of the fact that until our premises are more firmly established little that is dependable can be expected. It is equally clear, however, that more active effort should be made to utilize what is known, and the present case is an attempt at discovering a clue on which more elaborate work may be based.

It was desirable that bacteriological studies be undertaken in the present connection, but as this is a formidable undertaking, and was impracticable when contemplated, simpler methods were resorted to.

In feeding great numbers of organisms by the mouth, as is done with buttermilk, one would expect that they would reappear in the feces in equal or greater numbers; but this could not be postulated, least of all in the face of clinical improvement. One could not assume that a vast increase in the total number of bacteria within the gut, of whatever kind, could be beneficial or even harmless. It seemed interesting, therefore, to determine if possible what the facts might be in this regard.

Various methods have been advanced for the estimation of the fecal bacteria, but all of them are open to the criticism of inaccuracy.

Strasburger and Schmidt were among the pioneers in this work, but there is grave doubt whether their gravimetric method of centrifugalization or any of its later modifications is of any avail. It has met with disfavor at many hands, though championed by a few, the strongest of whom seem to be MacNeal, Latzer, and Kerr.[4] According to them it is possible by a most painstaking and laborious technique to obtain dependable results, but the present writer was forced by experience to the conclusion that any method which depends upon removal and estimation of the fecal bacteria by centrifugalization is unreliable.

MacNeal and others agree, however, that the method which admits of the nearest approach to accuracy is that of directly counting the organisms. Several modifications of this can be practised, the most available of which seems to be by mixing a

[4] Proc. Soc. Exp. Biol. and Med., New York, 1908-09, vi, 88 to 90.

known quantity of the properly diluted feces with a small amount of citrated normal blood, and, after agitating the whole, counting the ratio of organisms to red cells in a given stained smear. This gives an approximate idea of the number of organisms present, and while having little or no absolute value, is probably dependable in the same hands for relative values of wide variation.

The stools then when passed were at once covered with a solution of 0.5 per cent. HCl and thoroughly mixed to ensure contact of the acid with all parts. They were then sent to the laboratory and worked up as soon as practicable, generally within an hour. More acid of the same strengh was added to make a fairly liquid mass, which was then thoroughly rubbed up in a large mortar until of a uniform homogeneous consistency. This was further diluted if necessary, well mixed, then measured, mixed again, and a sample of 5 c.c. taken and diluted to 50 c.c., with the acid solution. A little of this mixture was drawn up in a small capillary tube. An equal amount of a mixture of normal human blood and sodium citrate was then drawn up into the same tube and the two solutions were mixed by blowing in and out on a glass slide. Smears were then made of this, fixed, and stained with Tiedmann's stain (methylene blue and eosin). A definite field of the slide was then chosen and a count made of 500 red blood cells and of the organisms in the same fields. Having used normal human blood with 5,000,000 red blood cells to the cubic millimeter, the proportion follows: 500 is to 5,000,000 as the number of organisms counted is to x, whence the final calculation is easily made.

By this means the total number of the bacteria of the stools for the first and the second periods were respectively as follows: Period I, 373,750,000,000; Period II, 12,372,000,000,000. This shows a marked increase in the total number in Period II. It was to be expected perhaps, and yet it could not be assumed until proved.

It is to be noted that the stools, in which the bacteria were counted in Period II, were natural or the result of an enema of salt solution, and did not represent colonic washings if they could be kept separate. It was evident before making the final calculation for dilution that in all cases the counts of bacteria were actually higher than in Period I. These counts were made by Dr. Glenn, resident pathologist of the Presbyterian Hospital, to whom the writer desires to express his indebtedness.

The true significance of this finding is not clear, since we know nothing of the types of organisms concerned.

It does seem reasonably apparent, however, that in joint conditions of this kind the mere presence of bacteria in greatly increased numbers within the bowel is not incompatible with improvement, and that these bacteria may play an important role to this end. Since the marked increase in the number of organisms is presumably due to the fermentative or lactic acid type the coincident increase of the ethereal sulphates is hard to explain, and lacking further

data one can merely hypothesize. Further experiments are in progress, with the view of substantiating these observations and determining their significance.

SUMMARY. Summing up the general facts indicated by this as yet incomplete study, it is evident that certain joint cases which are rebellious to all other means of treatment, as proved by long trial, can be arrested by means of a proper dietary coupled with colonic lavage.

The dietary can be so greatly modified during the course of improvement as eventually to differ but slightly from that of a normal individual, and the lavage can be quickly dispensed with entirely.

Coincident with the improvement there may occur an increased output of ethereal sulphates and an increased output of fecal bacteria. The former of these is not out of consonance with the view suggested by certain clinical evidence that the carbohydrates are of hitherto unsuspected importance in this connection. The way is opened to more careful study along this line.

There can be no doubt that while the principles on which the above treatment is based are perhaps known to some, they are unfamiliar if not unknown to the vast body of clinicians who attempt the treatment of this omnipresent disease.

Furthermore, there can be no serious question that a definite proportion of these sufferers can be benefited if not cured in this manner, and it is not inconceivable that further study will show most of them to be in this category.

The adoption of these methods should not be attempted except in cases suitably prepared for it or in those free from demonstrably removable cause. These methods should be applied gradually, with due respect for the caloric needs of the individual, and with constant regard for the weight. Only the most painstaking attention to detail will ensure success, and carelessness during or after convalescence will induce relapse.

The careful study, metabolic and otherwise, of cases which improve under this regimen must yield data of real value in deciphering the factors causing joint disease and the means of removing them.

The data here cited seem to form a suggestive beginning.

In conclusion it is a duty and pleasure to express obligation in a number of directions: To the late Dr. John H. Musser, to Dr. S. S. Stryker, Dr. James E. Talley, and Dr. Edward H. Goodman for many courtesies shown in the wards of the hospital; to Dr. Damon B. Pfeiffer, director of the pathological laboratory, for his courteous and obliging coöperation under hampered conditions; to the Board of Managers of the Presbyterian Hospital for the installation of chemical equipment for clinical research; and finally to Dr. Joseph Sailer, through whose interest and coöperation primarily the facilities for the present study were made possible.

THE HEALING OF GASTRIC AND DUODENAL ULCERS WITH BISMUTH.[1]

By Charles D. Aaron, Sc.D., M.D.,

PROFESSOR OF GASTRO-ENTEROLOGY AND ADJUNCT PROFESSOR OF DIETETICS IN THE DETROIT COLLEGE OF MEDICINE; CONSULTING GASTRO-ENTEROLOGIST TO HARPER HOSPITAL, DETROIT.

Bismuth was used as a medicinal agent as far back as 1786, when Oidier in Geneva recommended it as an infallible remedy for "stomach cramps;" and it has ever since asserted its place in the therapy of gastric affections. As a matter of course, Oidier used bismuth subnitrate (magisterium bismuti) quite empirically, without having any knowledge of the pathological anatomy of gastric ulcer or other gastric affections. He found that the bismuth salt had an anodyne effect upon gastric pains, and this discovery was sufficient to ensure its use, regardless of the exact pathology—which, indeed, could not in those days be clearly diagnosticated. About the middle of the nineteenth century Hannon[2] recommended bismuth as an antacid, giving, however, the preference to the subcarbonate. Oppolzer[3] likewise emphasized its antacid effect, and Bricka[4] referred particularly to the astringent effect of the drug upon the gastric mucosa.

It was left for Kussmaul to systematize the therapeutics of bismuth, following certain reflections on the pathological anatomy and physiology involved. His leading train of thought assumed this form: The irritating and painful sensations of gastric ulcer are caused by food remnants settling down at the base of the ulcer, irritating the latter as well as the exposed nerves, and thus causing acid formation and nausea. This can be easily understood as regards old and deep ulcers with elevated margins and incontractible base; and the mere passing of the gastric contents over small and superficial ulcers was held to be sufficient to cause pain. Although these food remnants can be removed by lavage, natural or artificial, this process will not prevent the constant formation of fresh deposits; so the idea suggests itself of providing a covering for the lesion which would protect it from irritation by the passing food. The same requirement follows from a consideration of the healing process. This takes place from the margins, forming granulating tissue toward the base, protecting the ulcer from irritation, and gradually closing the defect. This granulating tissue is very

[1] Read before the annual meeting of the American Gastro-enterological Association at Atlantic City, N. J., June 3 and 4, 1912.

[2] Presse méd., 1856, Nos. 46 to 50.

[3] Zeitsch. d. K. K. Gesellschaft der Aerzte, Wien, January, 1857.

[4] Cited after Rodari, Experimetelles u. Klinisches z. Kenntnis der Beeinflussung der Magensaftsekretion durch Medikamente, Volkmann's Sammlung klin. Vorträge, 1908, Innere Medizin, Nos. 144 to 146.

vulnerable, especially on the fibrous base of old and large ulcers, so that it falls an easy prey to either mechanical irritation by the ingested food or to the digestive action of the stomach. Therefore, this granulating tissue should be protected if possible—shielded from mechanical or chemical injury, just as a surgeon bandages a granulating wound in order to allow the natural healing process to take its course undisturbed.

Starting from these considerations, Kussmaul laid bismuth under tribute as the best means of securing the desired result. His expectations were realized. In many cases the pathological picture changed with surprising suddenness on the application of bismuth. Patients with old and deep ulcers, who experienced but slight relief from simple irrigations, were suddenly freed from pain; they could partake of food again, enjoyed once more an undisturbed night's rest, recovered their general health in a remarkably short time, and increased in weight. There is no longer a doubt that bismuth has a favorable effect upon the pain and the healing process in gastric and duodenal ulcer. The question now arises, how this favorable effect is to be explained, and whether Kussmaul's premises when introducing the remedy were correct.

The research work on this subject, comprising numerous clinical, anatomical, and experimental studies, has furnished proof of the fact that the protection afforded by bismuth subnitrate in gastric and duodenal ulcer is both physical and chemical.

It has been demonstrated by experiments on dogs, notably those of Matthes,[5] that a few hours after its administration bismuth is evenly distributed over the gastric wall. When the gastric contents were artificially removed, it was found that a protective layer of bismuth similar to a powder bandage had formed on the base of the ulcer. Occasional autopsy findings have shown the same effect in man. From clinical observation, too, it would appear that the bismuth deposit remains undisturbed for days upon the gastric mucosa. Fleiner[6] found that up to two or three days after the introduction of a bismuth suspension, bismuth remnants mixed with mucus could be recovered by lavage. Bismuth, as shown by the *x*-rays, can remain in the stomach for that length of time. This coincides with the statements of patients in regard to the length of their pain-free periods. After the first introduction of bismuth they are often free from pain during the day and the ensuing night, and sometimes longer.

All these observations have demonstrated the fact that, owing to its physical consistence, its fine distribution, and its high specific gravity, bismuth is capable of forming a layer over the ulcer which mechanically protects it from injury. Possibly, however, this effect

[5] Zentralbl. f. innere Med., 1894, No. 1: Beiträge z. pathol. Anatomie u. allgem. Pathol. 1893, No. 2.

[6] Münch. med. Woch., 1902, No. 23.

is not purely mechanical, but due in part to chemcial action. Matthes found that bismuth, when introduced into the stomach, induced a mucous secretion, and that the protective layer was a muco-bismuth mixture. In this process bismuth is reduced to bismuth oxide, and it may be assumed that this is the principal agent in the formation of the bismuth crust.

There is no doubt that bismuth possesses chemical properties, but it cannot yet be definitely stated whether the physical or the chemical property predominates in the relief of pain and the healing of the ulcer. The physical effect is produced by the entire quantity of bismuth introduced, whereas the chemical effect is dependent upon only a small portion of it. Bismuth subnitrate being insoluble in water is chemically inert under ordinary circumstances. A small part of the total quantity introduced in the stomach is decomposed in the acid gastric juice or duodenum, liberating nitric acid, and it is only after this process has taken place that the chemical action of the bismuth begins.

The chemical action of bismuth within the stomach and duodenum is (1) antisecretory, (2) astringent, and (3) antispetic. For the better understanding of these three bismuth effects, it is necessary to appreciate the chemical process which takes place upon the disintegration of the bismuth in the hydrochloric acid gastric contents. The decomposition of bismuth subnitrate takes place according to the following formula:

$$Bi\begin{matrix}NO_3\\O\end{matrix} + HCl = HNO_3 + Bi\begin{matrix}Cl\\O\end{matrix}$$

It has been found that the effective constituent is not the bismuth oxide thus formed, but the simultaneously liberated nitric acid; the three chemical effects above mentioned are due to this factor.

The antisecretory effect of bismuth is best illustrated by an experiment of Rodari[7] upon dogs with a Pawlow fistula (Experiment 15). The experiment may be tabulated as follows:

200 c.c. of water introduced at 7.30 A.M.		200 c.c. of water + 10 gm. bismuth subnitrate (= 5 per cent.) introduced at 1.30 P.M.	
Time.	Quantity of gastric juice.	Time.	Quantity of gastric juice.
8.00 A.M.	3.2 c.c.	2.00 P.M.	2.5 c.c.
8.30 A.M.	2.4 c.c.	2.30 P.M.	0.2 c.c.
9.00 A.M.	2.0 c.c.	3.00 P.M.	0.2 c.c.
9.15 A.M.	1.6 c.c.	3.30 P.M.	0.0 c.c.
9.30 A.M.	0.8 c.c.		
9.45 A.M.	0.0 c.c.		
Period of secretion, 1¾ hours.		Period of secretion, 1½ hours.	
Total quantity of secretion, 10 c.c.		Total quantity of secretion, 2.9 c.c.	
Total acidity, 150.		Total acidity, 120.	

[7] Verhandlungen des Kongresses f. innere Med., 1893.

The other experiments took a similar course.

Rodari distinguishes between the following effects of bismuth subnitrate upon the gastric mucosa:

1. *Healthy Mucosa.* Typical inhibition of secretion, the quantity and probably also the quality of the secretion being reduced. This reaction of a healthy gastric mucosa is the ordinary contingency following the introduction of bismuth subnitrate.

2. *Healing.* Owing to its astringent property, bismuth is capable of producing a direct healing effect. As is well known, astringents precipitate albumin and mucus, entering into combination with the albumin and forming albuminates. This process is particularly favored in the mucous membranes. As a result of the deposition of new, firm particles (the newly formed albuminates) in the tissue interspaces, the epithelial surface is smoothed (condensed) and the size of the bloodvessels diminished. Secretion is, therefore, still further reduced, and the hyperemic conditions and attendant pains are relieved; and the fact that mucous membrane of this consistence is an unfavorable culture ground for bacteria supplies another reason for the subsidence of the inflammatory manifestations. The astringent effect of the bismuth should, however, be only superficial; the result of a deeper action would be tissue destruction or corrosion. The bismuth subnitrate having been decomposed in the acid gastric juice, it is the simultaneously liberated nitric acid which produces the astringent effect. This astringent process is one of the mildest, but may be made to last a long time, since only a small amount of bismuth is decomposed at a time, and the total quantity remains in the stomach for hours together; the dose, however, should be repeated often enough to supply the loss from disintegration. Thus it is possible, with the aid of bismuth, to maintain a uniform gently astringent process for weeks and months.

3. The *antiseptic* effect of bismuth subnitrate, illustrated in surgery by the use of this salt as a dusting powder, is applicable also in gastric and duodenal ulcer—the remedy cleansing the ulcerous base and ensuring a practically antiseptic healing of the ulcer.

The following indications have been gathered from practical experience for the application of bismuth subnitrate in practice:

The first consideration is that it is always desirable to do without any medication whatever in the treatment of gastric ulcer and duodenal ulcer. As a matter of fact, bismuth can never be regarded as a substitute for the rest cure in the treatment of ulcer. Its general purpose is to reinforce this treatment, especially when the latter fails, or when the ulcer takes a chronic course, tends to relapse, or gives rise to considerable pain; and, furthermore, in the treatment of outdoor patients. If in these cases there is hyperacidity, bismuth is so much the more indicated, for it is more effectual in hyperacid cases than in others. Bismuth is least

indicated in cases marked by achylia or subacidity; in the total or comparative absence of hydrochloric acid in the stomach it cannot be decomposed, and its efficiency is restricted to the exercise of its physical properties. From this it follows that bismuth subnitrate is not to be looked upon as a specific for gastric and duodenal ulcer. Its successful application depends principally upon individualization and manner of use. The chief requirement is to have the protective layer over the ulcer large and resistant from the first, and to renew and supplement it at regular intervals. As soon as the subjective complaints are relieved, the daily bismuth dose may be tentatively reduced and, as the treatment proceeds, administered only every second day. If there should be no trouble on the day that bismuth is withheld, the intervals may be extended until finally the treatment is discontinued entirely. In consideration of what has been said about the physical and chemical action of bismuth, it is evident that it should only be administered finely suspended in a liquid medium.

As mentioned before, the practical application of bismuth has extended considerably since Kussmaul's publications on the subject, and has been further generalized and simplified by his pupil Fleiner.[8] At first, Fleiner used the following method of treatment:

The stomach being washed out, as soon as the irrigation fluid returned clear without acid reaction 10 to 20 grams of bismuth subnitrate, well mixed with 150 to 200 c.c. of tepid water, was poured through the funnel. As the tube slowly emptied itself, it was carefully withdrawn, after which the patient was immediately placed in the position corresponding to the seat of the ulcer—in the right decubitus if the ulcer were seated at the pars pylorica, and in the recumbent position if there were reason to believe that the ulcer occupied the lesser curvature.

In order not to inconvenience the stomach too much by the volume of water, Fleiner frequently left the clamped tube in the stomach for a while, until the heavy bismuth had settled, and then, before slowly withdrawing the tube, allowed part of the water to flow off.

According to his present method, the stomach tube is discarded entirely and bismuth suspensions (10 to 20 grams of bismuth subnitrate in a tumbler of warm water) are taken by mouth, in the morning, on an empty stomach, the latter having been cleansed three-quarters of an hour to an hour previously with about 150 c.c. of Carlsbad or Vichy water. The bismuth is given daily, the dose, as before mentioned, being more or less rapidly increased, reduced, or discontinued, according to the clinical course.

The quality of the bismuth preparation used is important. According to Fleiner[9] the best preparation is bismuth subnitrate

[8] Zeitsch. f. klin. Med., 1904, vol. lii.

[9] Loc. cit.

which has been precipitated from a boiling hot mixture, as this is much more finely powdered than a preparation precipitated from tepid or cold fluids.

A modification of this method consists in administering bismuth in oil by combining the bismuth treatment with Cohnheim's oil treatment — which is indeed a very practical and successful method. The doses of bismuth stated above are taken, finely suspended in olive oil, several times daily. According to Stepp,[10] bismuth suspensions in chloroform water are very efficacious:

	Gm. or c.c.
℞—Bismuthi subnitratis	3
Chloroformi	1
Aquæ destillatæ	150

M.—Sig.—One to two tablespoonfuls to be taken hourly for several weeks.

It is not unlikely that the chloroform conduces to the anodyne effect. The several methods for the application of bismuth in the treatment of gastric and duodenal ulcer have been fully described by me.[11]

There is no denying the fact that the bismuth treatment is attended with some disadvantages. Liberal and prolonged administration of bismuth is not infrequently followed by constipation, which has to be relieved either by enemas or by a combination of the bismuth with magnesium oxide. It is equally possible that, under certain circumstances, large doses of insoluble bismuth will, in passing through the intestinal tract, cause diarrhea. Nor does every stomach tolerate large quantities of bismuth. In one case bismuth has led to concrement formation in a cavity of the stomach formed by perforation of the ulcer into the pancreas (Fleiner). In a few rare cases intestinal calculi have been formed through the influence of bismuth (Wegele[12]).

There have also been cases in which the bismuth crust became so indurated and was so firmly consolidated with the ulcerous base that the ulcer underneath was prevented from healing, the crust acting like a foreign body. Cases of this kind are not very frequent, but they have occasionally been seen in autopsies and operations. Thus, Naunyn reports the case of a patient who died of gastric hemorrhage, and autopsy showed the gastric ulcer to be covered with a bismuth crust weighing about 20 grams.

A further objection, raised by Elsner, and certainly not without justification, is that the stomach may not have sufficient tonic power to bear a preparation as heavy as bismuth subnitrate administered in large doses and for a long time. Elsner attributes

[10] Berlin. klin. Woch., 1893, p. 983.
[11] Diseases of the Stomach, Lea & Febiger, Philadelphia, 1911, pp. 442 to 446.
[12] Die Therapie der Magen und Darmerkrankungen, Jena, 1905.

the frequently observed constipation to weakness of the intestinal musculature, caused by the heavy bismuth.

All these disturbances, which will occasionally arise, should be considered when deciding upon bismuth treatment. In short, it is necessary to adapt the treatment to the individual case.

Direct failures of the bismuth treatment have been reported by Elsner,[13] Boas,[14] and Zweig.[15] These authors freely acknowledge the anodyne effect of bismuth, but do not think much of its curative effect.

Unfounded reports have been made of poisonous manifestations following the use of bismuth. Fleiner[16] states that, in 1829, Justinus Kerner published the history of a fatal poisoning by subnitrate of bismuth, but later, in 1835, the fact was established that the poisoning resulted not from bismuth, but from hydrargyrum præcipitatum album. It was this erroneous publication of Kerner's that gave bismuth a bad name, from which it has not yet entirely recovered. Other reports on poisoning by bismuth are, in all probability, attributable to the use of impure preparations, containing arsenic and lead. Chemically pure bismuth subnitrate is non-poisonous.

Boas[17] prefers the subcarbonate to the subnitrate, Hannon[18] having previously called attention to bismuth subcarbonate, as mentioned above. The subcarbonate is non-poisonous and probably has the same general effect as the subnitrate, including the antacid effect. An advantage of bismuth subcarbonate is that it colors the feces white, thereby facilitating the recognition of any coarse admixture of blood. Bismuth subnitrate, on the other hand, colors the stool black or greenish black through the formation of bismuth oxide, which may either lead timid patients to erroneously suspect hemorrhage, or conceal an actually existing hemorrhage. An objectionable feature of bismuth subcarbonate is that, on entering into combination with hydrochloric acid of the stomach, it releases a certain amount of carbon dioxide, which under certain circumstances may give rise to considerable distention of the gastric wall and the ulcer. Besides, the beneficial effect of the liberated nitric acid is lost.

Bismuth subgallate is a very acceptable substitute for bismuth subnitrate. It can be freely suspended in water and is non-toxic, but its constipating effect is greater than that of bismuth subnitrate. It can be suspended not only in water, but, as recommended by Ageron,[19] in oil to advantage.

[13] Lehrbuch der Magenkrankheiten f. Aerzte und Studierende, 1909, Berlin.
[14] Diagnostik und Therapie der Magenkrankheiten, 1907, Part II. Leipzig.
[15] Die Therapie der Magen und Darmkrankheiten, Berlin-Wien 1907.
[16] Loc. cit. [17] Loc. cit. [18] Loc. cit.
[19] Münch. med. Woch., 1902, No. 30.

CONTRIBUTION TO THE BACTERIOLOGY OF PERITONITIS, WITH SPECIAL REFERENCE TO PRIMARY PERITONITIS.[1]

By Morris Fishbein, M.D.,
CHICAGO.

(From the Pathological Laboratory of Rush Medical College, Chicago.)

The purpose of this report is twofold: (1) To discuss the records in the pathological laboratory of Rush Medical College of bacteriological examinations made of material obtained from the peritoneal cavity after death from peritonitis, and (2) to compare the results of this analysis with other similar summarizing reports on the bacteriology of peritonitis.

In a rather thorough search of the literature the only statistical reviews of a similar nature of the bacteriology of peritonitis, as it may be studied by examination of peritoneal fluids made after death, including any considerable number of cases, are those of Flexner[2] and Manahan.[3]

The examinations made in the pathological laboratory of Rush Medical College were undertaken for the most part by students as a part of their routine work and under careful supervision. The postmortem examinations were held in the Cook County Hospital, the Presbyterian Hospital, and in a number of other hospitals in Chicago; a few were in private homes or in undertaking establishments. The report of Flexner includes a summary of the cases observed in the Johns Hopkins Hospital up to 1897 and that of Manahan the records of the Massachusetts General Hospital up to 1905. As the records of the pathological laboratory cover a period of approximately thirteen years previous to 1911, each report overlaps the preceding one by six years.

Anatomically, peritonitis in the records I have studied has been divided into purulent, serofibrinous, fibrinous, acute septic, hemorrhagic, fibrinopurulent, and seropurulent types. Of each form there were: Purulent, 64; serofibrinous, 64; fibrinous, 33; acute septic, 11; hemorrhagic, 6; fibrinopurulent, 6; seropurulent, 2.

The anatomical character of the inflammation does not bear any relationship to the nature of the primary lesion when such exists, nor does it seem to be influenced by the presence of various

[1] Read before the Chicago Pathological Society, April 8, 1912.
[2] Philadelphia Med. Jour., 1898, ii, 1019.
[3] Boston Med. and Surg. Jour., 1905, cliii, 346.

bacteria alone or in combinations of various kinds. Various bacteria or the same bacteria cause the same or different forms of peritonitis, and a similar lack of relationship exists between such disease conditions as pneumonia, cholecystitis, appendicitis, salpingitis, etc., in so far as the features of the peritonitis are concerned. In these respects the conclusions arrived at from a study of the records I have examined are confirmatory of those previously made by Flexner and Manahan.

In classifying my records of cases of peritonitis I have used the classification proposed by Flexner in 1898, which seems for all purposes the best possible in that it is simple, distinct, and a real expression of clinical and bacteriological etiology. Previous to that time the classification of Tavel and Lanz[4] proposed in 1893 was the one commonly used. These authors divided all peritonitides into primary and secondary types; the former including blood and lymph infections and being mono-infectious, that is, with one organism, and the latter all other cases, and being polyinfectious. Flexner divided all cases of peritonitis into primary, exogenous, and endogenous types. Primary peritonitis occurs as a result of previous chronic diseases or an infectious focus elsewhere in the body, the infecting organism being brought by the blood or lymph channels to the peritoneum. Exogenous peritonitis occurs as a result of wound infection from gunshot wounds, abortion with sepsis, septic instruments, etc., and includes laparotomies with subsequent peritonitis. Endogenous peritonitis occurs as a result of organisms coming from foci in relation to the peritoneal cavity, the most common cause being various affections of the appendix. Further division is then made into pure and mixed types where one or more than one organism is found.

In the following table, which includes all cases of peritonitis in the Rush records, in which bacteriological examinations were made, is given the classification and number of cases of each type, the organisms found, and their frequency in pure and mixed infections.

[4] Mitteilungen aus klin. u. med. Inst. der Schweiz, 1893.

TABLE I.

Organisms	Primary			Exogenous			Endogenous			Total
	Pure	Mixed	Total	Pure	Mixed	Total	Pure	Mixed	Total	
Colon bacillus	3	10	13	1	2	3	27	40	67	83
Streptococci	5	7	12	..	2	2	3	18	21	35
Staphylococci	3	9	12	1	2	3	4	29	33	48
Pneumococci	5	4	9	..	1	1	2	5	7	17
Gas bacillus	1	..	1	..	..	..	..	1	1	2
Bacillus proteus	..	..	..	..	..	..	1	2	3	3
Bacillus mucosus	..	1	1	..	..	..	..	2	2	3
Typhoid bacillus	..	..	..	..	..	..	3	3	6	6
Bacillus pyocyaneus	..	1	1	..	..	..	1	1	2	3
Bacillus paratyphosus	..	..	..	..	..	..	1	..	1	1
Micrococcus tetragenes	..	1	1	..	..	..	..	..	..	1
Unidentified	..	..	..	..	..	..	2	1	3	3
Sarcinæ	..	..	..	..	..	..	..	1	1	1
Bacillus cloacæ	..	..	..	..	..	..	..	3	3	3
Combinations:										
Colon bacillus and streptococcus	..	2	2	..	..	..	..	6	6	8
Colon bacillus and staphylococcus	..	1	1	..	..	..	..	10	10	11
Colon bacillus and pneumococcus	..	2	2	..	1	1	..	1	1	4
Colon bacillus and typhoid bacillus	..	..	..	..	..	..	..	1	1	1
Colon bacillus and bacillus pyocyaneus	..	..	..	..	..	..	..	1	1	1
Colon bacillus and Micrococcus tetragenes	..	1	1	..	..	..	..	..	..	1
Colon bacillus and bacillus cloacæ	..	..	..	..	..	..	..	2	2	2
Colon bacillus and gas bacillus	..	..	..	..	..	..	..	1	1	1
Colon bacillus and bacillus proteus	..	..	..	..	..	..	..	2	2	2
Colon bacillus and bacillus mucosus	..	1	1	..	..	..	..	1	1	2
Colon bacillus and sarcinæ	..	..	..	..	..	..	..	1	1	1
Streptococci and staphylococci	..	3	3	..	1	1	..	7	7	11
Streptococci and pneumococci	..	1	1	..	..	..	..	..	..	1
Staphylococci and pneumococci	..	..	..	..	..	..	..	1	1	1
Staphylococci and typhoid bacilli	..	..	..	..	..	..	..	1	1	1
Staphylococci and bacillus pyocyaneus	..	..	..	..	..	..	..	1	1	1
Multiple organisms	..	3	3	..	1	1	..	8	8	12
Totals	17	15	32	2	3	5	44	45	89	125

In the report of Flexner a protocol or short summary of the anatomical diagnosis in each case is given; Manahan classified all

his cases according to various rather well-defined anatomical causes. In the following table I have recorded the significant point in the anatomical diagnosis in each case included in the postmortem records of the pathological laboratory of Rush Medical College, and have followed to some extent the outline of Manahan.

TABLE II.

Sources of peritonitis.	Type.	Cases.
Cause not found or suppurating foci at points distant from peritoneal cavity	Primary	18
Salpingitis	Endogenous	20
Terminal peritonitis in pneumonia	Primary	18
Perforation of small intestine	Endogenous	17
Carcinoma of stomach	Endogenous	15
Following laparotomy for other than suppurative conditions in peritoneum	Exogenous	15
Typhoid ulcer with or without perforation	Endogenous	13
Appendiceal abscess	Endogenous	11
Extension from adjacent suppuration	Endogenous	10
Perforated appendix with abscess	Endogenous	9
Carcinoma of genito-urinary tract	Endogenous	5
Carcinoma of large intestine or rectum	Endogenous	5
Puerperal uterus	Endogenous	4
Perforation of large intestine	Endogenous	4
Carcinoma of pancreas	Endogenous	3
Colotomy	Endogenous	3
Extra-uterine pregnancy	Endogenous	3
Ulcerative cholecystitis	Endogenous	2
Abscess of bladder wall	Endogenous	2
Gangrenous pancreatitis	Endogenous	2
Ruptured liver abscess	Endogenous	1
Perforation of uterus	Endogenous	1
Sarcoma or abdomen	Endogenous	1
Intestinal obstruction	Endogenous	1
Hemorrhagic pancreatitis	Endogenous	1
Abortion	Endogenous	1
Gastric ulcer, operated	Endogenous	1

This includes in all 184 cases, of which there are 39 primary, 16 exogenous, and 129 endogenous. It is at once apparent that there may be considerable overlapping in such a division of sources and some difficulty in determining the classification in one or two cases.

A comparative study of the results included in the three tabulations has been of considerable interest in many respects. It has afforded an insight into the advance of bacteriological study, with facilitation of technique; it has enabled us to arrive more accurately at the true value of various factors involved because of the greater numbers of cases thus brought together, and has enabled us to eliminate any factors determined in the different studies of this nature, which might seem to be related to the various types of material found in special localities. In the following table are included 106 cases summarized by Flexner, 110 cases summarized by Manahan, and 126 cases included in the records I have analyzed in which bacteriological studies were made.

TABLE III.

	Rush.	Flexner.	Manahan.	Totals.
Total number of cases	126	106	110	342
Organisms:				
Colon bacillus	83	55	45	183
Staphylococcus	48	27	8	83
Streptococcus	35	54	54	143
Pneumococcus	17	8	12	37
Typhoid bacillus	6	3	0	9
Bacillus proteus	3	6	0	9
Bacillus mucosus	3	0	12	15
Bacillus cloacæ	3	0	0	3
Gas bacillus	2	8	1	11
Bacillus pyocyaneus	2	6	0	8
Micrococcus tetragenes	2	0	0	2
Bacillus (lactis) aërogenes	1	0	0	1
Bacillus paratyphosus	1	0	0	1
Unidentified	3	8	2	13
Types of infection	126	106	110	342
Pure infection	63	55	51	169
Mixed infection	63	47	37	147
Primary, pure	17	9	7	33
Primary, mixed	15	1	2	18
Exogenous, pure	2	25	10	37
Exogenous, mixed	3	9	5	17
Endogenous, pure	44	21	34	99
Endogenous, mixed	45	37	30	112

"Unreliability of statistics" is an extremely trite phrase. This triteness is in itself an expression of the truth of the statement. Nevertheless, reports of large numbers of cases have in the past resulted in much valuable information, especially in regard to etiology and the results of treatment; they have in many cases indicated prophylaxis. Even after making such full and liberal allowances as can best be made only by one who has labored with such statistics as these, it has seemed to me that some generalization was justifiable.

From the facility and ease with which the cases have been brought under Flexner's classification, it seems proper to point out again that for all purposes such a classification as that proposed by Flexner is to be preferred. It suggests at once both the clinical and bacteriological etiology of the peritonitis, and the route of infection must be of primary importance in the classification of the condition.

The bacteriological results given in Table I were determined by students in the department of pathology of Rush Medical College. During the first half of the thirteen years covered by the records, cultures were made from colonies obtained on plates of plain agar. Since that time the technique has been as follows: Fluids are withdrawn in sterile pipettes and transmitted as soon as possible to the laboratory, where tubes of agar, melted and cooled to 43° C., and mixed with about 8 drops of human defibrinated blood, are inoculated with two dilutions. These are poured into plates and

subcultures are made from colonies developing on these plates. While the results do not indicate by the number and types of organisms found any overwhelming superiority in this latter method, they seem to show that the identification of the organism is made quicker and more often by the latter method. The results included in Flexner's report as well as those of Manahan represent bacteriological studies made by men in all probability better trained in this work. The comparative study of the various results has therefore been of great interest, and seems to show in gross, great similarity.

For the reason that both previous reports included the various combinations in which organisms were found, such a procedure was followed here, although it seems to offer but little in the way of valuable information as to the bacteriological etiology of peritonitis. Occurrence of various organisms in symbiosis is of importance, and in this regard it is worthy of note that both in these records and those reported by Flexner the Bacillus pyocyaneus was found together with the colon bacillus, although Dudgeon and Sargent,[5] in a report made in 1905, affirm as a result of numerous experiments, that this is not possible.

The colon bacillus was found 183 times in 342 cases. Its importance as a factor in the bacteriology of peritonitis will at once be conceded, but the point of interest is as to whether it occurs singly in any large proportion of cases or is usually associated with some other organism. Flexner found 11 single infections and 44 multiple, Manahan found 12 single and 33 multiple, and I have found 31 pure and 52 multiple. We must therefore conclude that the colon bacilus most commonly occurs mixed with other organisms and that it may quite often occur singly. Further analysis shows that it is seldom if ever a blood infection, and that in all cases of primary peritonitis where the colon bacillus is found it is probably the second invader.

The staphylococci, according to the records of the Rush Pathological Laboratory, occur more commonly than would seem to be the case from the reports of Flexner and Manahan. It is generally known that the staphylococcus may often be a contaminating organism in amateurish bacteriological work. However, in the report of Dudgeon and Sargent, which includes records of bacteriological examinations of peritoneal fluids taken at the time of operation, the staphylococcus was found in 108 of 270 cases. This seems to be the only report of this character in the accessible literature, and it would seem to indicate that a large proportion of staphylococci in peritoneal fluids is to be expected rather than not.

As a virulent organism commonly associated with septicemia, the importance of the streptococcus as a causative factor in peritonitis, especially the primary type, is at once apparent. Its occurrence

[5] Lancet, 1905, i, 473.

in cases of peritonitis where a septicemia is present is shown by Manahan, who found septicemia present in 32 of 110 cases, the streptococcus being present in 24, pneumococcus in 5, and the staphylococcus in 2. From the cases included in Table I it was found that the pneumococcus was of more importance than the streptococcus as regards the association of peritonitis with a septicemia.

In none of the reports was record made of the presence of the gonococcus in peritoneal fluids examined post mortem.

The relative importance of the pneumococcus in recent years is well expressed by the numerical ratio shown by the records of Flexner, Manahan, and the Rush records respectively. It seems to be particularly associated with primary peritonitis, and the literature of the last few years contains many reports of primary pneumococcic peritonitis.

The typhoid bacillus occurs in peritoneal fluid in cases of peritonitis where there is a perforation of the small bowel or where no such perforation exists. All these cases have been classified as endogenous, although, as is obvious, some may have been primary, or all, in which no perforation was found, may have been primary.

Bacillus mucosus is of importance as shown by the figures given, and the gas bacillus is a common finding in all cases of feculent peritonitis.

The majority of all cases of peritonitis are endogenous in character and are due to a combination of the colon bacillus and other organisms, usually staphylococci and streptococci.

Exogenous peritonitis occurs much less commonly with perfecting of operative aseptic technique and with lessening of exploratory laparotomy, instrumental abortion, etc.

The records of the Rush Laboratory include 39 cases of primary peritonitis in 184 cases, or 25 per cent., as contrasted with 10 per cent. in the reports of Flexner and Manahan. Primary peritonitis, which includes blood and lymph infections, both from infected foci elsewhere in the body or from previous chronic disease, or all cases apparently idiopathic, forms a larger proportion of acute cases than is commonly supposed. For this reason and because of the interest attached to this subject a further analysis was made of all cases coming under this classification and a rather thorough search of the astonishingly meagre recent literature was undertaken with a view to summing up the reports to the present time.

Primary Peritonitis. In the decade from 1870 to 1880 the subject of idiopathic peritonitis received considerable attention from various writers (Collie,[6] Lewis,[7] Meade,[8] Semple[9] and others), who advanced various theories as to its origin without any actual basis upon which to found their conclusions. They considered the

[6] Med. Exam., London, 1877, ii, 843.
[7] Trans. Med. Soc. New York, 1873, p. 143.
[8] British Med. Jour., 1876, ii, p. 393.
[9] Med. Exam., London, 1878, iii, 553.

subject from a purely clinical standpoint, and attempted to solve the origin of the condition, finally associating it with sleeping in a draught, catching cold, etc.

Flexner, in 1897, called attention to the classification of Tavel and Lanz, previously mentioned, and the relation of the apparently idiopathic peritonitis to blood and lymph infections, when a previous chronic disease occurred in an individual, or where there was an infectious focus elsewhere in the body.

Nothnagel,[10] in 1901, argued against such an hypothesis, but stated "that the last word on this subject must come from the pathologist, not the clinician." He states that in 13 cases reported by Grawitz from a total of 867 none would bear close criticism. To him it was clear that although theoretically any causes acting on the pericardium, pleura, or meninges to set up inflammation might act as well upon the peritoneum, careful scrutiny would reveal in all supposedly primary cases some endogenous source for infection. He mentioned a case in which a patient caught cold, the tonsils being found much infected with a form of streptococcus. In a subsequent supposedly primary peritonitis the same type of organism was found. The explanation advanced by Nothnagel is that the patient swallowed mucus containing these streptococci, and that they gained their entrance to the peritoneum through the stomach wall rather than by a blood or lymph infection. In view of the results of modern investigation with recovery of organisms from the blood in similar cases these suggestions of Nothnagel become of interest only in a historical way.

Armstrong[11] in 1903 found 5 cases of primary peritonitis in 102 autopsies. Osler in an analysis of 102 autopsies from earlier records found 12 cases. "In every instance," says Armstrong, "the subject was a female." In 2 instances the streptococcus was found, in 1 the pneumococcus, and in 2 no bacteriological studies were made. The fact that all these cases occurred in females seems to suggest to Armstrong that the uterus and Fallopian tubes were the mode of entrance of the organisms. In other words, they would be exogenous rather than primary. He also suggested that a *locus minoris resistentia* in the peritoneum may be established by shutting off the blood supply, not uncommonly by caseating tuberculous retroperitoneal lymph glands, and bacteria brought by the blood, or through the pleura or tubes set up an infection.

The opinion of Spencer[12] in a report in which he discusses several cases of apparently idiopathic peritonitis is that in every instance the bacteria must come from the intestines or stomach or other organs within the abdominal cavity. He does not consider the blood or lymph routes of infection as possibilities.

[10] Wien. med. Presse, 1901, xlii, 1321.
[11] Montreal Med. Jour., 1903, xxxii, 728.
[12] Westminster Hosp. Rep., London, 1907, xv, 18.

In a report of several cases by Sheldon[13] in 1902 the work of Hawkins, who showed that an appendix may appear perfectly normal and still contain minute abscesses which give rise to infection, is supported. Sheldon concludes that in all cases of apparently idiopathic peritonitis, organisms gain access to the peritoneum from the intestines or other organs within the abdominal cavity.

Of the 39 cases of primary peritonitis in 184 cases included in the Rush records in 18 instances a pneumonia was present. In order to make clear the conditions existing in the other cases a short abstract of the chief points in the anatomical diagnosis of each case is given.

Case I, No. 630.—Acute serofibrinous peritonitis. Micrococcus tetragenes; colon bacillus. Cardiac hypertrophy; emphysema and purulent bronchitis; acute and chronic pleuritis and empyema; cirrhosis of the liver, with gummas; cholelithiasis; chronic gastric catarrh.

Case II, No. 732.—Acute serofibrinous peritonitis. Bacillus pyocyaneus; colon bacillus. Chronic tuberculous cavities in the lungs; chronic disseminated pulmonary tuberculosis; marasmus.

Case III, No. 859.—Acute serofibrinous peritonitis. No bacteriological study made. Premature birth; congenital syphilis; double white pneumonia; osteochondritis.

Case IV, No. 938.—Diffuse fibrinopurulent peritonitis. Micrococcus tetragenes; colon bacillus; Streptococcus pyogenes. Hyperplasia of lymphoid tissue in intestinal canal; emphysema and atelectasis of lungs; cloudy swelling of liver and of kidneys; acute splenitis; hypertrophy of left ventricle; hypoplasia of aorta; tonsils enlarged, dark red, and soft on section.

Case V, No. 959.—Fibrinous peritonitis. No bacteriological study made. Enlarged retroperitoneal and mediastinal lymph glands; right fibrinous pleuritis; edema of lungs; interstitial myocarditis; chronic inflammation of the gall-bladder; hypertrophy of tonsils.

Case VI, No. 966. Diffuse fibrinopurulent peritonitis. Staphylococcus albus. Vaccination wound of right leg; suppurative adenitis of right deep inguinal and iliac glands; purulent infiltration of retrocecal tissue.

Case VII, No. 996.—Fibrinous peritonitis. Gas bacillus. Puerperal uterus; general invasion of gas-producing organisms.

Case VIII, No. 1059.—Serofibrinous peritonitis. No bacteriological study. Small white kidney; acute bronchitis, with abscess formation in adjoining lung tissue.

Case IX, No. 1133.—Fibrinopurulent peritonitis. Staphylococci. Fibrous and fibrinous pleuritis; acute vegetative aortic endocar-

[13] Med. Record, 1902, lxii.

ditis; acute splenitis; puerperal uterus; hyperplasia of lymphoid tissues in intestines.

CASE X, No. 1262.—Purulent peritonitis. Colon bacillus. Multilobular fatty atrophic cirrhosis of liver; icterus; ascites; arteriosclerosis (slight); dilatation of esophageal and hemorrhoidal veins.

CASE XI, No. 1312.—Fibrinous peritonitis. Streptococcus. Acute aortic endocarditis; organizing fibrinous pericarditis; cardiac dilatation and hypertrophy; fibrinous pleuritis.

CASE XII, No. 1349.—Fibrinopurulent peritonitis. Pneumococcus; colon bacillus. Fatty degeneration of heart and kidneys; goitre.

CASE XIII, No. 1613.—Serofibrinous peritonitis. No bacteriological study made. Atrophic cirrhosis of liver; dilatation of esophageal veins; chronic endocarditis.

CASE XIV, No. 1645.—Fibrinous peritonitis. Staphylococci. Atrophic cirrhosis of liver; ascites; general anasarca; icterus; chronic valvular and mural endocarditis; chronic pleuritis; postmortem fat necrosis in pancreas.

CASE XV, No. 1636.[14]—Serofibrinous peritonitis. Colon bacillus; staphylococcus. Generalized blastomycosis.

CASE XVI, No. 1692.—Serofibrinous peritonitis. Pneumococcus. Seropurulent arthritis of knee-joint; acute mediastinitis; acute hyperplastic splenitis; hyperplasia of intestinal lymphoid tissue.

CASE XVII, No. 1701.—Fibrinous peritonitis. Colon bacillus; streptococci. Diabetes; gangrene of toe; acute nephritis; tuberculosis of sacro-iliac synchondrosis; chronic mural endocarditis; suppurative sternoclavicular synovitis; psoas abscess.

CASE XVIII, No. 1734.—Serofibrinous peritonitis. No bacteriological study made. Atheromatous ulcers of aorta, with multiple thrombi; embolism of superior mesenteric artery; infarction of small intestines; multiple foci of necrosis in pancreas.

CASE XIX, No. 1768.—Serofibrinous peritonitis. Streptococcus. Acute hyperplastic tonsillitis. Hyperplasia of all lymph glands; small localized abscess in right lower lobe of lung; edema of larynx.

CASE XX, No. 1802.—Fibrinous peritonitis. Colon bacillus; streptococcus. Puerperal uterus; septic endometritis, suppurating corpus luteum of pregnancy.

CASE XXI, No. 1808.—Serofibrinous peritonitis. Streptococcus. Chronic parenchymatous nephritis; pleuritis; chronic pericarditis; cystitis; gastritis.

In 18 cases, as already stated, pneumonia existed, with large numbers of pneumococci in the lung and circulation. In 7 cases there was an associated endocarditis, chronic in type, and often also pleuritis. In 4 cases hyperplasia of lymphoid tissue was marked.

[14] E. E. Irons and E. A. Graham. Jour. Infect. Dis., 1906, iii, 666.

In 4 cases suppurative foci were present elsewhere in the body, distant from the peritoneum. Besides these, there was 1 case of marasmus in tuberculosis, 1 case of premature birth with congenital syphilis, and a case of generalized blastomycosis. In 3 cases a cirrhosis of the liver was present.

A tonsillar lesion is believed often to form the point of entrance for organisms which bring about an endocarditis or pleuritis, and grouping together the cases in which there were endocarditis and hyperplasia of the lymphoid tissue in the throat we find that the streptococcus was found four times, the staphylococcus twice, and in 2 cases no bacteriological studies were made. In the 12 cases of primary peritonitis reported by Flexner the streptococcus was found five times and the staphylococcus twice. The inference that some relationship exists is fully justifiable, and after pneumonia such a condition as this might well be looked for in all cases of supposedly primary idiopathic peritonitis.

The case of terminal peritonitis in congenital syphilis in an infant is of interest because of the not uncommon occurrence of such peritonitis as the causal factor of death in infants whose resistance is lowered. Thus Holt[15] reports a fibrinopurulent peritonitis of unknown origin in a male child, aged six months, in whom the streptococcus was isolated from the peritoneal fluid, and mentions 6 other cases in his own experience. Dr. H. F. Helmholtz[16] has described to me 3 cases which he examined thoroughly and in which he could find no demonstrable source for infection. In such instances it might well be that bacteria had passed from the throat to the blood and thence to the peritoneal cavity.

SUMMARY. Peritonitis would seem therefore in the light of the results here given to be most commonly associated bacteriologically with a combination of the Bacillus coli and other organisms, usually staphylococci and streptococci. The origin clinically is usually endogenous, affections of the appendix being of major importance, the female organs of generation being next in importance. Exogenous peritonitis is becoming exceedingly rare with improvement of aseptic technique in the handling of wounds and in operative methods.

As has been mentioned, but one complete report of bacteriological conditions in peritonitis at the time of operation is available. The work of Dudgeon and Sargent gives conclusions somewhat at variance with those determined by postmortem examinations of peritoneal exudates, and should therefore be confirmed, with a view to arriving at the relation between the condition existing at the time of operation and that found post mortem. In connection with this point it is of extreme interest to note that

[15] Arch. Pediatrics, 1906. xxiii, 278.

[16] Personal communication.

recently the question of the relation of anaërobic bacteria to appendicitis particularly is attracting much attention. Runeberg[17] and Heyde[18] have shown that in many instances of appendicitis anaërobes predominated over aërobic bacteria and agglutinated with the patient's serum in higher dilutions. Other writers, basing their conclusions upon similar experiments, state that Bacillus coli is of most importance etiologically (Kotzenberg[19] and Klienberger[20]). It would seem therefore that both aërobic and anaërobic cultures and determinations had best be made in all instances.

The gonococcus has never been demonstrated culturally in peritoneal fluids post mortem according to the various reports of large numbers of cases. By the clinical history in many instances we are led to believe that the gonococcus is the exciting cause of many peritonitides. In all probability, therefore, its presence has not been shown because of lack of development in cultivating methods or because no special efforts have been made to secure it. Because of its great clinical importance this fact should not be overlooked in future work of this nature.

Primary peritonitis is more common than is ordinarily supposed. In this report 25 per cent. of all cases are of the primary type. Each of these cases is a subject for investigation. In practically all cases there is a lowered resistance of the individual due to some chronic condition, as atrophic cirrhosis of the liver, chronic endocarditis and tonsillitis, marasmus, diabetes, etc. In such conditions the resistance of the peritoneum must be lowered to such an extent that where ordinarily the highly resistant tissue might combat infection with organisms carried by the blood stream, in such instances it becomes the seat of an acute peritonitis which may prove fatal unless proper handling be undertaken after the condition is recognized. In other conditions where a suppurative focus exists elsewhere in the body, or where an infected puerperal uterus, or acutely infected tonsils pour virulent bacteria into the blood stream, we have the other factor for a terminal or acute infection of the peritoneum—namely, a virulent organism. In still other cases, where we have both virulent organisms in large quantity and a lowered resistance of the individual, we may readily have a condition resembling an endogenous peritonitis, where through rupture of an appendix, for example, large quantities of bacteria and toxic material are poured out upon an intact peritoneum, the latter lowering its resistance and the former setting up an acute peritonitis. It would seem then that the word "idiopathic" could be entirely dispensed with in regard to peritonitis, as mani-

[17] Studien über die bei peritoneal Infectionen appendik. Ursprungs vorkommenden Sauerstofftoleranten sowie oblig. anaerob. Bacterien formen. Arb. a. d. path. Inst. d. Univ. Helsingforis. Berlin. i, 271, 1908.

[18] Beitr. zur klin. Chir., 1911, lxxvii, 1.

[19] Deut. med. Woch., 1909, xxxv, 201.

[20] Deut. Arch. f. klin. Med., 1907, xc, 267.

manifestly close scrutiny yields some source for the condition. The bacteria gain entrance to the peritoneal cavity and the inflammation of the peritoneum is a manifestation of their presence. In the absence of a known exogenous or a demonstrated endogenous source it is important to determine whether any means by which the organisms gained entrance into the blood or lymph stream is demonstrable.

THE PROGNOSTIC SIGNIFICANCE OF THE ATROPINE REACTION IN CARDIAC DISEASE.[1]

By James E. Talley, M.D.,

VISITING PHYSICIAN TO THE PRESBYTERIAN HOSPITAL, PHILADELPHIA.

My interest in the influence of the vagus on the rate of the heart beat was awakened last year while working in Dr. James Mackenzie's wards in the Mt. Vernon Hospital, London. For the many courtesies shown me by Dr. Mackenzie, Prof. Cushny, Dr. Marris, and other co-workers in the clinic I am deeply grateful. The work on which this paper is based was done largely during my term of service last year in the Presbyterian Hospital, Philadelphia. I appreciate the kindness of my colleagues of the medical staff who placed material at my disposal. It is regrettable that suitable material and the necessary leisure to use it so often fail to come together in point of time.

The recapitulation of a few facts concerning the normal physiological influence of the vagus on the rate of the heart beat may not be out of place. Stimulation of one or both vagi by a rapidly interrupted induction current slows or stops the heart. Such vagal stimulation lessens the conductivity, but does not destroy the irritability of the heart, since direct strong mechanical stimuli may provoke a beat even during cardiac standstill due to vagal stimulation. Conversely, section of one vagus produces some acceleration of the pulse; section of both vagi causes greater acceleration. These phenomena are constant in the vertebrates and prove that the vagi are the normal paths by which travel continually restraining impulses from the inhibitory centres in the medulla to the heart. Physiologists have also found it a constant experience that atropine produces a decided increase in the cardiac rate by paralysis of the vagi. Clinicians find that a hypodermic injection of grain $\frac{1}{50}$ to grain $\frac{1}{25}$ of atropine produces the same effect. Physiologists have further shown that atropine acts on the vagi, and not on the muscular substance of the heart, by the observation

[1] Read before the College of Physicians of Philadelphia, March 6, 1912.

that in early embryos, so young that no nerves have yet grown to the heart, the drug has little or no effect.[2]

After making dozens of injections of atropine, grain $\frac{1}{75}$ in robust males, and grain $\frac{1}{50}$ in females and less robust males, the writer has yet to see any untoward effect, or hear any decided complaint. The patient should be told that the throat will become dry, and ability to read may be lost for part of the day. Almost always the patient is ready for the next meal, rarely complains of insomnia, and the following day reads as usual. The same has been true in those cases of rebellious hemoptysis where the same doses of atropine have been used.

Professor Cushny suggested the releasing of the vagus by means of hypodermic doses of atropine, so-called atropine reaction, in the study of digitalis action. Silberberg[3] made use of it in studying the action of digitalis in cardiac disease, especially auricular fibrillation. His paper will be referred to later. The method of taking the reaction is thus: The recumbent patient is made as comfortable as possible, the arm supported on a pillow or folded sheet, the ink polygraph applied to the right radial, the engine started at slow speed, and the pulse rate taken graphically for about ten minutes, so as to obtain an average pulse rate before atropine. Throughout the minutes are marked off by touching the time marker every minute by the watch. This makes a slight break in the line, which simplifies the counting later. The hypodermic of atropine is now given in the other arm, while the engine is still running, and the pulse rate taken continuously for another fifty to sixty minutes. The influence of the drug, ordinarily dry throat, may appear as early as twelve to fifteen minutes, but on the average in twenty minutes. The maximum is usually reached in from twenty to thirty minutes from the time of injection, and usually there is no further rise after this or at least after the hour. Just how long the influence may last I have not had time to determine, but in a few cases, when taken at three to five minute intervals, during the second hour there has been no further rise. Counting the pulse rate from the long rolls of paper and setting them down in order in a column shows at a glance when the maximum is reached. The graphic representation by means of loci curves (Fig. 1) shows the contrasts better. The pulse rate before atropine is the average for the ten minutes before the hypodermic. The reaction or the pulse rate after the atropine is determined in this paper by taking the average for ten minutes when the pulse rate is at its maximum after the injection.

The writer started out with two ideas: One was to determine the atropine reaction in hearts as normal as the material available

[2] Halliburton, Handbook of Physiology, p. 256.
[3] Proc. Royal Soc. Med., iv, 192 (1910–1911).

furnished. Of course, the medical wards of a hospital are not ideal places to look for absolutely normal hearts, yet many are approxi-

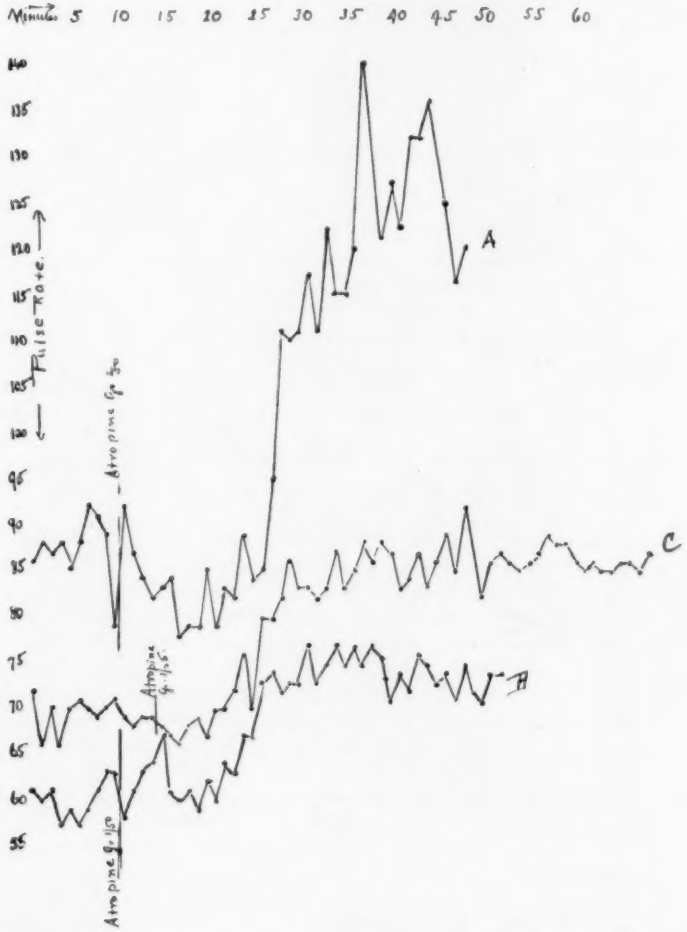

FIG. 1.—Curve *A* represents the influence of atropine, grain $\frac{1}{50}$, in Case I, Table II, before digitalis. Curve *B* represents the influence of atropine, grain $\frac{1}{50}$, in Case I, Table II, on full digitalis. Curve *C* represents the influence of atropine, grain $\frac{1}{25}$, in Case No. 14, Table I.

mately so. The individual outside with a perfect cardiovascular apparatus is not keen to lend himself to such determinations, because it may mean loss of time if the atropine happens to paralyze

accommodation. Having obtained four reactions in persons with approximately normal hearts, there was no difficulty in obtaining plenty of contrasting material, as will be shown by Table I. The other idea was to use the reaction in the study and treatment of patients with cardiac disease. Unfortunately too many of the availabe cases were of the regular pulse type. However, several studies will be embodied in Table II.

TABLE I.—The patients in Table I, except the last four, had at least no gross lesions of the heart. Nos. 1 and 4 were apparently entirely normal, and Nos. 2 and 3 were so far from their original attacks as to be practically so. They were having extension or superheated air for the old lesions in the joints. Taking these 4, though inadequate, I know, for a working basis, we may look upon the normal reaction as from 30 to 40. The actual average of the 4 is 34. The next ten observations were made in patients who had grossly normal hearts, however these hearts had all been subjected to a chemical poison (No. 5), or the toxines and fever of enteric (Nos. 6 to 10). As the pulse rate, the vagal influence being withdrawn, depends upon the inherent activity of the rhythm giving portion of the heart, it was expected there might be a difference in reaction, and, broadly speaking, this was found true. The exhausted cardiac tissue showed a lessened rather than an increased irritability. Observation 5a was clear when the fault in technique was discovered. In 5b the small reaction is probably due rather to the toxic material in the circulation, due to the acute kidney irritation, than to any influence of the possibly absorbed bichloride of mercury itself on the heart muscle. This view is supported by the normal reaction obtained in observation 5c, the kidneys having cleared up in the two weeks intervening. All the enteric cases (Nos. 6 to 10) give a reaction that is less than normal. In cases Nos. 6 and 7, though a week intervened between the two reactions in each case (6a and 6b, and 7a and 7b), the second reaction was less than the first in each case (6a, 24; 6b, 18; 7a, 24; 7b, 17). One would have expected that after a week, the heart having recovered somewhat, the reaction would have been greater rather than less. The same thing is evident in taking the whole group. The longer a patient has had a normal temperature, the higher the reaction does not follow. For example, Case 10, with temperature normal thirty days, gives a reaction of 12, while 6a and 7a, with normal temperature for seven and nine days respectfully, give each a reaction of 24. The small reaction of these enteric cases reminds one of the similar reaction in the senile cardiosclerosis cases. Here the morbid processes leading to slight response are probably but temporary, while the degenerative process in the cardiosclerosis cases are permanent.

TABLE I.

No.	Sex.	Age.	Diagnosis.	Blood Pressure.	Date.	Pulse rate before atropine.	Pulse rate after atropine.	Full vagal effect.	Dose of atropine.	Throat dry. Minutes.	Remarks.
1	F.	18	Hysteria	116—80	October 10	102	132	30	1/25	20	Patient well.
2	F.	21	Old gonorrheal arthritis (hand)	120—60	September 21	95	121	26	1/50	23	No fever for one month.
3	M.	25	Old gonorrheal arthritis (knee)	111—65	October 20	71	111	40	1/25	30	Acute attack months before.
4	F.	48	Gastroptosis	145—75	November 20	89	129	40	1/50	18	Patient admitted for operation.
5a	M.	24	Acute corrosive sublimate poisoning	130—75	September 27	73	68	..	1/25	..	Tablet undissolved in syringe.
5b	M.	24	Acute corrosive sublimate poisoning	..	September 28	77	93	16	1/33	20	Urine full of albumin and casts.
5c	M.	24	Acute corrosive sublimate poisoning	134—60	October 11	61	101	40	1/25	18	Urine practically normal.
6a	M.	35	Enteric fever	110—60	October 6	66	90	24	1/25	25	Seventh day of normal temperature.
6b	M.	35	Enteric fever	120—70	October 14	100	118	18	1/25	15	Fifteenth day of normal temperature. Patient up and around.
7a	F.	34	Enteric fever	100—55	November 29	104	128	24	1/50	20	Ninth day of normal temperature.
7b	F.	34	Enteric fever	..	December 6	114	131	17	1/50	17	Sixteenth day of normal temperature. Patient up and around.
8	M.	29	Enteric fever	125—60	October 17	89	109	20	1/25	24	Tenth day of normal temperature.
9	M.	21	Enteric fever	120—57	October 2	113	120	7	1/25	20	Fourteenth day of normal temperature. Patient up and around.
10	F.	18	Enteric fever	..	September 30	99	111	12	1/50	18	Thirtieth day of normal temperature. Patient up and around.
11	F.	29	Small tumor pressing on right vagus	..	June 21	66	130	64	1/50	19	Bradycardia; extrasystoles.
12	M.	45	Mitral disease; auricular fibrillation	125	August 11	101	115	14	1/25	20	
13	F.	26	Mitral disease; auricular fibrillation	..	July 28	109	143	34	1/50	20	
14	M.	60	Cardiosclerosis	170	August 19	70	87	17	1/25	16	Extrasystoles; auricular and ventricular; P-R normal.
15	F.	22	Mitral and aortic disease	108—90	September 29	68	99	31	1/50	25	Pulse always regular; venous pulse, auricular type.

TABLE II.

No.	Observation.	Sex.	Age.	Diagnosis.	Blood pressure.	Date.	Pulse rate before atropine.	Pulse rate after atropine.	Full vagal effect.	Full digitalis effect.	Vagal factor in digitalis.	Tissue factor in digitalis.	Dose of atropine.	Amount of digitalis taken.	Throat dry. Minutes.	Remarks.
Ia	Before digitalis	M.	35	Mitral stenosis; auricular fibrillation	..	June 7	90	130	40	..	..	..	1/50	..	27	
Ib	Full digitalis	M.	35	Mitral stenosis; auricular fibrillation	..	June 21	61	75	..	29	14	55	1/50	ʒ14	18	
Ic	Before digitalis	M.	35	Mitral stenosis; auricular fibrillation	..	July 3	95	145	50	..	..	..	1/25	..	45	Two doses, grain 1/50, atropine; second half-hour after first.
Id	Full digitalis	M.	35	Mitral stenosis; auricular fibrillation	..	July 26	63	75	..	32	12	70	1/50	ʒ14	26	
IIa	Before digitalis	F.	20	Mitral disease; auricular fibrillation	..	June 15	112	148	36	..	..	..	1/25	..	20	
IIb	Full digitalis	F.	20	Mitral disease; auricular fibrillation	..	July 3	55	56	..	57	1	92	1/25	ʒ14	15	Two to one heart block.
IIIa	Before digitalis	M.	45	Mitral disease; auricular fibrillation	110—75	May 28	87	115	28	..	..	..	1/25	..	30	
IIIb	Full digitalis	M.	45	Mitral disease; auricular fibrillation	115—65	July 5	51	80	..	36	29	35	1/25	ʒ34	30	
IIIc	On digitalis	M.	45	Mitral disease; auricular fibrillation	85—55	June 13	85	117	..	2	32	0	1/25	ʒ 9	24	
IVa	Before digitalis	M.	35	Cardiosclerosis; auricular fibrillation	145	July 28	60	78	18	..	..	..	1/50	..	25	
IVb	Full digitalis	M.	35	Cardiosclerosis; auricular fibrillation	..	August 31	60	60	..	0	0	18	1/50	ʒ32	24	
Va	Before digitalis	M.	71	Cardiosclerosis; heart block	132—65	December 17	77	96	19	..	..	..	1/50	..	20	Phases of partial block and tachycardia before digitalis.
Vb	Full digitalis	M.	71	Cardiosclerosis; heart block	172—102	January 1	42	106	..	35	64	0	1/33	..[1]	20	
Vc	On digitalis	M.	71	Cardiosclerosis; heart block	..	December 23	80	82	..	..	2	14	1/50	..[2]	20	
VIa	Before digitalis	M.	14	Heart sound; after pneumonia	95—45	December 23	73	103	30	..	..	..	1/50	..	25	Six days after crisis.
VIb	On digitalis	M.	14	Heart sound; after pneumonia	102—50	January 6	74	114	..	0	40	0	1/50	ʒ 7	24	

Infusion 15 ounces; digitalone, ʒv.

[1] Infusion 7 ounces.

Case 11 was a patient of Dr. W. E. Robertson's, with whom I took her atropine reaction. She had a small tumor either involving, or at least pressing upon, the right vagus, which gives her a bradycardia. Her pulse during the day we took the reaction had been 36. The emotional disturbance of having a new procedure tried was probably responsible for the average rate of 66 before the atropine. The reaction of 64 reminds one of the response often given by cases of auricular fibrillation with a high pulse rate before atropine. In such cases the bundle is supposed to be in a highly irritable condition, and to carry too many impulses from the disorderly auricle. That her heart was irritable is shown by the great number of extrasystoles in the tracing even during the time she was under the influence of atropine. Atropine more often abolishes the extrasystoles. Dr. Robertson will report the case in full probably after operation. The remaining cases (Nos. 12 to 15), though they are patients with definite cardiac lesions, are included more naturally in Table I, as they were not taken after full digitalis also. They will be referred to later.

TABLE II.—The capital paper of Silberberg has already been mentioned. He shows the prognostic significance of the atropine reaction in cardiac cases especially auricular fibrillation, and how it may be used in the study of digitalis action. My cases add nothing new, but are simply fresh illustrations of some of the facts set forth by him. Now let us compare the atropine reaction in some of these fibrillation cases before they are given any digitalis, or any treatment except rest in bed. First of all cases of cardiosclerosis, both those with regular pulse and those developing auricular fibrillation, especially if they have a slow rate, most often give a small reaction to atropine. There are exceptions. Table II, IVa, reaction 18, and Va, reaction 19, are illustrations of the first statement. Table I, No. 12, though his initial pulse was 101 gave a reaction of only 14. Table I, No. 14, whose sclerosis was unmistakable, with no fibrillation, gave the same small reaction, 17 (Fig. 1, *C*). Speaking broadly, it is unusual for cases giving such small reactions to respond well to digitalis, and thus the reaction carries prognostic significance.

On the other hand, patients with rheumatic mitral disease developing auricular fibrillation with rapid pulse rate, give large atropine reactions, normal or above (Fig. 1, *A*). Thus Table II, observations Ia, Ic, IIa, IIIa give reactions of 40, 50, 36, and 28 respectively, that is, practically normal or above. Silberberg had 4 patients who under simliar circumstances gave reactions of 44, 53, 60, and 53. Thus, we see different cases, or groups of cases, give widely varying reactions under atropine. The pulse rate, the vagal influence being abolished, depends upon the activity of the pace-making part of the heart, that is, it depends upon either stimulus production or conduction. Just which is probably

incapable of proof, however, Silberberg's explanation seems more likely. He looks upon the bundle as being highly irritable in these fibrillating hearts with rapid pulse rate, and as carrying an excess of stimuli from the disorderly auricle to the ventricle. Thus a large atropine reaction probably means an irritable bundle, a small reaction some defect in the bundle.

Now let us turn to the role the atropine reaction may play in the study of the action of digitalis on the heart. First of all, let us briefly enumerate a few of the well recognized facts concerning the therapeutic action of digitalis. Digitalis produces the most decisive slowing of the pulse in those cases of old rheumatic mitral diseases which have developed auricular fibrillation, especially with rapid pulse rate. Digitalis has but little influence on hearts the seat of senile cardiosclerosis, especially with a slow pulse, even though they develop auricular fibrillation.

Patients with a regular rhythm rarely show any such marked response as the first group above. Of course, it is recognized that digitalis may produce a slowing in these cases, but never is the therapeutic effect so brilliant as in the first group. Now the question arises, how does digitalis slow the heart, especially in these cases of auricular fibrillation where the response is so decisive. The possibilities are: Increased vagal inhibition, sinus slowing, depressed conductivity (blocking), and possibly a direct nutritional influence on the whole heart. That is, it must act through the vagus, or on the heart itself, influencing some or all of its functions.

Prof. Cushny suggested that the atropine reaction might be used to eliminate the vagal factor in the digitalis slowing, and thus determine whether it is a large, a constant, or a varying factor. To determine this Silberberg studied 12 cases, mostly auricular fibrillation, in the Mt. Vernon Hospital, and the writer has a few to add.

The patients, having been in the hospital long enough to eliminate the possibility of drug influence from medicines taken before admission, on rest alone, had their atropine reaction taken according to the method described. They were then put on a good preparation of digitalis, usually the tincture, minims 15 to 20, three times a day, and kept on it until they showed their limit of tolerance, anorexia, headache, nausea, and possibly vomiting. Now the reaction was taken again and the results compared.

The group of cases of auricular fibrillation (Table II, Ia, Ic, II, III) show marked slowing under digitalis. A study of the pulse tracings of this group (Fig. 2) shows how the digitalis slowing is produced. Many small beats disappear, the remaining are more even in height, and the diastolic pauses more regular. Turning to the tracings of this same digitalized group when given atropine we find that many of the small beats reappear at the expense of the diastolic pauses as the pulse accelerates. The type in both

instances remains that of auricular fibrillation. The inference is that under digitalis increased vagal influence has prevented many

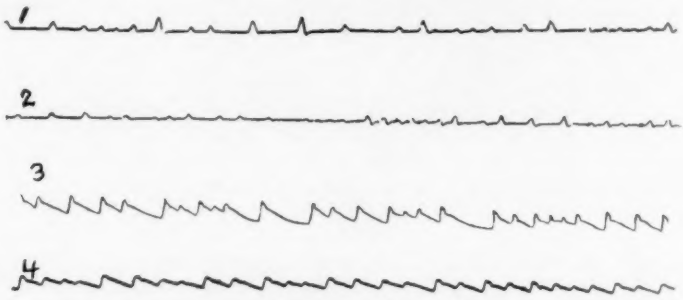

FIG. 2.—Showing character of pulse tracings in auricular fibrillation, Case III, Table II. Unfortunately, unintentionally the tracings of the patients giving larger reactions were destroyed. 1, before any treatment, pulse rate 90; 2, twenty minutes after injection of atropine, grain $\frac{1}{75}$, pulse rate 126; 3, full digitalis (drams 34); pulse rate 55; 4, forty minutes after injection of atropine, grain $\frac{1}{75}$; pulse rate 86; patient under full digitalis.

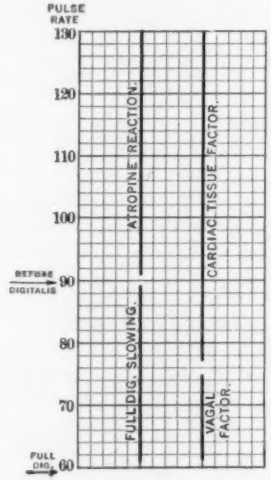

FIG. 3.—Silberberg's diagram adapted to Case I, Table II. The initial pulse before any treatment except rest was 90, and under atropine rose to 130. He was given full digitalis, and his pulse fell to 61. While under full digitalis the reaction was again taken but the pulse rate increased only from 61 to 75, a reaction of 14 which is the vagal factor in the digitalis slowing. Then 130 minus 75 or 55 represents in figures the increment of improvement in the cardiac muscle or the cardiac tissue factor.

stimuli from getting through. Remove this vagal influence by atropine, and again the fibrillating auricle sends through a rabble of impulses. Again we note in this group under atropine in digitalis

action the pulse rate not only does not reach the height attained under atropine before digitalis was given, but falls short of even the initial rate before any treatment whatsoever. If the vagal factor were the only element in the slowing we should expect to see the atropinized pulse rate reach the same height after digitalis, as it did before. Hence, there is evidently a second factor concerned in the slowing, which is probably the direct result of the digitalis on the heart itself, or the bundle, and is probably nutritional. These factors have been referred to as the vagal factor and the cardiac tissue factor. Their relationship will be most easily understood by referring to Fig. 3. These factors vary in different cases. The following tabulation will make the matter plainer:

Case.	Ia	Ic	II	III	IV	V	VI
Full vagal effect	40	50	36	28	18	19	30
Full digitalis slowing	29	32	57	36	0	35	0
Vagal factor	14	12	1	29	0	64	40
Cardiac tissue factor	55	70	92	35	18	0	0

In the first 4 cases the tissue factor is by far the greater. This is in accordance with their clinical history, their cardiac tissue was capable of great improvement under digitalis. They are the cases which get well enough to resume at least a part of their ordinary activity. Case II had a bundle most susceptible to digitalis which easily produced blocking. Case IV is typical of the experience with the well developed cardiosclerosis case. They can be promised little improvement under treatment. Case V, a patient in Dr. Sailer's service, showed the average slowing, but it was entirely vagal. He showed no improvement under atropine used therapeutically, nor under digitalis, and succumbed later with dilated heart and pulmonary edema. Case VI was the only post-pneumonic patient available at the time. His sound heart and normal pulse argued that digitalis would have no effect as it proved, but the toxin of pneumonia did not impair his response to atropine as it did in the typhoid cases.

Conclusions. 1. The atropine reaction in the normal heart is probably from 30 to 40.

2. A reaction of 20 or less, in a heart not recently subjected to exhausting disease, points to a degenerative process in the cardiac tissue which makes the outlook for improvement under treatment unpromising.

3. Cases of auricular fibrillation with responses normal or above are promising subjects for treatment.

4. Two atropine reactions in cases of auricular fibrillation, one before and one on full digitalis, enable us to determine whether the vagal or the cardiac tissue factor is the greater. The patients with a large cardiac tissue factor are the ones who usually are sufficiently improved by treatment to return to their occupations.

THE THERAPEUTIC USE OF TUBERCULIN: A WORKING HYPOTHESIS AND SOME PERSONAL OBSERVATIONS.[1]

By Lawrason Brown, M.D.,

SARANAC LAKE, NEW YORK.

When I contemplated presenting to you my experience with tuberculin, my memory carried me back to the time some twelve years ago when I first began to use tuberculin under Dr. Trudeau's direction and inspiration. It is needless for me to say that I doubt if I would have begun its use at that time unless his faith had been so sure and strong that it was of some benefit. In 1900 Koch's original tuberculin had been in use nine years and his new tuberculin (T. R.) was some three years "old." Many modifications had already been tried: Hunter's, Trudeau's, etc.; Brehmer and Hahn had described their tuberculoplasmin and Klebs had learned at that time that antiphthisine did not fulfil his expectations. In 1900 I gave T. R. and a year later tuberculol of Landmann, a powerful poison which killed even normal guinea-pigs. The next year Koch described bacillary emulsion, and before long we were using that form of tuberculin. Since then I have used other forms of tuberculin, the broth filtrate, endotin, Beraneck's, old tuberculin, and mixtures of some of these forms.

To use any therapeutic means intelligently, to obtain its best results, and to advance the treatment of the disease by its exhibition, we should have in mind some reason for the faith that leads us to use it. I claim no originality for many of the following views which I have gathered from many sources, nor am I unaware that many objections, and some well founded, may be raised to these views, but they have afforded me a working hypothesis and as such I give them.

A Working Hypothesis. It is a well-known fact that normal animals do not react to tuberculin, and show, even after repeated doses, no sensitiveness to it as indicated by the ordinary tuberculin tests or reactions. The tuberculin reaction depends upon the presence of tuberculous tissue in the organism. The mere presence of dead or living tubercle bacilli in the body is not sufficient for a tuberculin reaction. The difference between normal and tuberculous animals lies in the fact that the latter possess tuberculous tissue, where is formed spontaneous tuberculin which in some way renders the animal sensitive to tuberculin. It is probable that normal animals possess no so-called receptors for tuberculin which is therefore inert when injected into their bodies.

[1] Read before the Section on General Medicine of the College of Physicians of Philadelphia, April 22, 1912.

These receptors, or antibodies, are probably first formed in the focal (epithelioid) cells of the tuberculous tissue, cells which owe their formation to the irritation of the tuberculous poison and would seem therefore to possess from the beginning receptors for the poisons that have called them into existence. These cells are phagocytic and ingest tubercle bacilli, some of which they break down. What part the serum plays in setting free the protein portion of the tubercle bacilli, which is the active constituent of tuberculin, cannot be determined. It is this tuberculous protein, this primary protein as we may call it, that in all probability, sensitizes the body cells and is found in greatest concentration in the tubercle.

At this stage we might consider that the tubercle is composed of focal (epithelioid) cells, which contain tubercle bacilli in all stages of disintegration, primary protein and primary protein which has been acted upon by complement, either through the agency of some intermediary substance or possibly alone. This secondary substance, which if we like we may call anaphylatoxin, is what is concerned with the general and febrile reaction. The central nervous system and the tuberculous foci are most sensitive to this poison which often produces marked depression without general reaction or the usual fever. This explains what happens in many chronic cases, when without much fever and without apparent reaction they gradually lose weight and falling into a state of malnutrition, die finally from asthenia. The primary tuberculous protein is capable of sensitizing or stimulating cells in other parts of the body through, I believe, some agency arising in the tubercle. We may call it receptor, antibody, or amboceptor to facilitate discussion. Arising first in tuberculous tissue in the focal cells, these antibodies are in greatest concentration in the focus but later in the course of the disease are formed in other parts of the body. It is probably through these antibodies or amboceptors, that the injected tuberculin and complement are drawn into or fixed in the focus, thus producing focal reaction. Complement may be present in such small amounts that some time must elapse before a sufficient amount is fixed to produce the local reaction. In certain methods of application (cutaneous and ophthalmic tests) the amount of tuberculin absorbed depends, *cæteris paribus*, upon the time the tuberculin is in contact with the skin or conjunctiva. If, as occurs in the subcutaneous injection of tuberculin, only a small fraction of it is fixed at the site of injection, the remainder is absorbed into the circulation.

These receptors are most numerous in the focus whither most of the injected tuberculin finally finds its way and is fixed by the receptors. The period of incubation, the time between the injection of tuberculin and the general reaction depends upon the time required to bring enough injected tuberculin and tuberculin

in the focal cells together with the antibody and complement to set free sufficient anaphylatoxin to cause the general reaction. The union in the focus produces the focal reaction which brings about the hyperemia.

In tuberculin treatment the quantity of tuberculin injected usually falls short of the quantity necessary to enable the complement to set free sufficient anaphylatoxin to produce a general reaction but does cause a focal reaction. These focal reactions stimulate the formation of antibodies some of which are thrown off into the blood stream. In a few cases they occur spontaneously, but more often they are found only after larger doses of tuberculin. Termed usually antibodies, they may be said to include agglutinins, precipitins, bacteriolysins, opsonins, and complement deviating substances (antituberculin), etc. These substances, however, have not yet been causally connected with clinical improvement, or indeed, with sensitiveness to tuberculin. When large doses of tuberculin are reached without reaction, that is, tuberculin tolerance is acquired, it is possible that some of the free antibodies may partially neutralize the injected tuberculin, so that larger doses are required to produce reaction in even the most acutely sensitive cells of the tuberculous foci, while the cells in other parts of the organism, needing a greater stimulus to produce a response, fail entirely to react. This "neutralization" of tuberculin may rest only in part upon the presence of antibodies, and may depend more upon the increasing lytic activity of the complement. By this I mean that the splitting of the tuberculous protein may be so great that the stage of anaphylatoxin is entirely passed over, which probably occurs during pancreatic digestion of protein. It may again be explained by the failure of the complement to split up the primary protein (the injected tuberculin) which then calls forth a superabundance of antibodies or amboceptors, which would lead later, with an efficient complement, to the more intense disintegration of the tuberculin. It is also of interest to note that in some patients, when tuberculin is beneficial, it seems to bring about improvement in symptoms almost with the first dose.

Now focal reactions may lead on the one side to absorption of tuberculous tissue, due no doubt to the greater blood supply there present at that time, an idea which is based upon Bier's work on the effect of hyperemia upon chronic inflammation. On the other side, they may produce demarcation, softening, and destruction of the focus, which in turn may lead to deposition of lime salts or replacement by fibrous tissue.

The failure of tuberculous individuals to react to tuberculin may be due to the neutralization of the injected tuberculin by the presence of antibodies in the body juices, or again to the failure of the body to produce complement in sufficient amount to cause

reaction, or rather to the production of complement which is not sufficiently lytic to split up the injected tuberculin.

Hypersensitiveness is difficult to explain. The facts are that after an overdose of tuberculin the patient may become extremely sensitive to greatly reduced doses. This would indicate either an increased formation of the split product of the tuberculin anaphylatoxin, or increased susceptibility of certain cells of the body to the poison. Now patients who are doing well clinically, as well as some with active or subacute symptoms, may both present this phenomenon, which appears therefore to be favorable as well as unfavorable. An increased formation alone of anaphylatoxin would account for its unfavorable action, but this alone can hardly be the only cause, for it must also be increased in the favorable cases. Here the immunity mechanism seems so adjusted that whatever spontaneous primary protein escapes from the focus is immediately disintegrated, that is, the lytic process, set up by the complement, is so active that anaphylatoxin is never formed, and the lysis carries the splitting process on to the formation of simpler bodies. Now when a sufficient amount, however small, of tuberculin (primarily protein) is injected into the body, it changes this favorable balance and the action is not carried on so far and anaphylatoxin results. If perchance through overexertion a focus is flooded or washed out by an increased blood flow, so much more primary protein than usual escapes that it cannot be split up beyond anaphylatoxin, general and focal reactions occur and recur, which today some call excessive auto-inoculation. To stem these is at times difficult, and their result is disastrous.

It has been held that tuberculin does not act like other proteins, such as serum or egg white, in the production of anaphylaxis. A minute quantity of horse serum, injected into an animal previously sensitized with it, produces anaphylactic symptoms. The second injection may be introduced in any way and anaphylaxis results. This is not true of tuberculin. When, for instance, a normal guinea-pig is sensitized with a small quantity of tuberculin, enough, for example, to produce a skin reaction in a tuberculous guinea-pig, which is 0.02 c.c., and a second small dose is injected into the skin, muscles, or peritoneum, nothing results. If, however, a larger dose is injected, or if a very small dose is injected into the cerebral cavity or intravenously, anaphylactic symptoms supervene.

Recent work has shown that serum is the most concentrated form of protein solution that we have. Attempts to concentrate the primary protein of the tubercle bacillus lead to the conclusion that the greater dilution of this protein may explain many of the differences in action between it and serum. There is, however, a further difference that must be noted. To bring about tuberculin anaphylaxis, strong concentrations of tuberculin must be brought in direct contact with the cells of the central nervous system.

THERAPEUTIC ADMINISTRATION. Turning now to the practical therapeutic administration of tuberculin, I might repeat what I said six years ago, namely, that the most important point in the tuberculin treatment is the dosage. At that time I predicted that the opsonic index would never be generally adopted as a guide to the individual dose. Since that time the cutaneous and ophthalmic tests have been widely employed, and some have made use of them in determining the individual dose, as I shall mention a little later.

Many sites of administration of tuberculin have been employed, such as the oral, rectal, vaginal, intratracheal, intravenous, cutaneous, intracutaneous, subcutaneous, and the inhalation methods. For one reason or another, the majority of these have been discarded, and tuberculin is now usually injected under or into the skin. The intravenous method has some possibilities, but Koch and his followers who made use of it were never very enthusiastic about it and few have employed it.

PREPARATIONS FOR ADMINISTRATION. How long tuberculin retains its strength in solution has never been determined. Strong solutions (7.5 per cent.) appear to retain some of their reacting powers at the end of two to three years. Weaker solutions may deteriorate much more quickly, and I have used dilutions, freshly prepared, every two weeks. As a diluent, $\frac{1}{4}$ per cent. phenol in physiological saline has been used, but the phenol can be replaced by lysol. A 10 c.c. cylindrical graduate, an ordinary tuberculin syringe, and a bottle of sterile physiological salt solution, preferably with a syphon or a stop-cock inserted at the side, enable one to make the dilutions in a very few minutes. Each dilution is $\frac{1}{10}$ the strength of the preceding.

The skin should be rubbed with alcohol and the needles sharpened each day before use. A very fine needle should be used.

VARIETIES OF TUBERCULIN. The forms of tuberculin which I have used might be grouped under three heads:

1. Those forms of tuberculin which consist of extracts of tubercle bacilli or substances secreted during their growth, if such exist. Koch's original tuberculin is the best example of this class. Among other forms I have used Landmann's tuberculol, Denys's broth filtrate, Beraneck's tuberculin, tuberculin A. F., Gabrilowitch's endotin.

2. Tuberculin composed of the body substance of the tubercle bacillus, of which I have used T. R. and B. E.

3. I believe I was the first to suggest the use of these two types of tuberculin together. A compound known as B. F. Co. consists really of a mixture of broth filtrate and bacillary emulsion in the proportion of 5 to 2 by volume. This form of tuberculin contains every product of the tubercle bacillus, unaltered by heat and theoretically appeals to me very much.

Practically, I might say that I have not noticed any difference in the action of the various types of tuberculin save that some are more poisonous than others.

Dosage. When I first began to give tuberculin in 1900 I used the doses advocated by the makers of the various tuberculins which I employed. Accordingly, for O. T., the first dose was 0.1 mg. ($\frac{3}{1}$), for T. R., 0.002 mg. ($\frac{5}{2}$),[2] and for B. E. 0.0025 mg. ($\frac{5}{2\,5}$) solid substance. Later it seemed to me that when much smaller beginning doses ($\frac{8}{1}$ or even $\frac{9}{1}$) were employed, the patients reacted to much smaller quantities of tuberculin. Anaphylaxis had not been described at that time, but certainly many patients seemed to exhibit marked susceptibility to very minute doses. More recently I have again employed larger beginning doses, and frequently give 0.000001 or even 0.00001. These doses cause no reaction in many patients, but a few become hypersensitive, and I am never able to increase the dose very much.

Methods of Administration. There are two methods of giving tuberculin which have different aims in view. The usual method, that described by Koch and modified by Trudeau and others, is to give a dose much below that required to produce a reaction, and by gradually increasing the quantity, to bring about immunity or better, tolerance, not to the tubercle bacillus, but to tuberculin itself. I have employed this method for years, but always realized that it fell far short of what was required for the most successful treatment. When the discovery of opsonins was announced I hoped that the opsonic index would give us the criterion that we needed to select at each injection the optimum dose. It is needless for me to say that the method presents too many difficulties, too many uncertainties, to enable it to be employed for such purposes. In many patients it is not difficult to bring about a marked tolerance to most tuberculin, and there is some evidence to show that patients who take tuberculin well have a tolerance to it which may have been established before tuberculin treatment had been begun. One patient recently received as an initial dose, 0.00001 ($\frac{4}{1}$) B. F., and in one hundred and fourteen days was given 33 doses, the last being 1000 mg. of B. F., without suffering a reaction or inconvenience at any time. The patient did very well, but was it on account of tuberculin? I question it. Others started about the same time have never been able to take a dose as large as this. They have not done so well.

Where tuberculin tolerance is wished, it seems to me safe to give, say $\frac{8}{1}$ O. T. in 0.1 c.c. of diluent, intradermically, and to increase the dose tenfold twice a week ($\frac{7}{1}$, $\frac{6}{1}$, $\frac{5}{1}$, $\frac{4}{1}$) until the local skin reaction begins to be marked. In one case with extensive

[2] "$\frac{5}{2}$" represents a convenient abbreviation for 0.000002 g. or c.c.

physical signs, good general condition, and few symptoms, I reached a subcutaneous dose of $\frac{3}{1}$ O. T. in six to seven weeks with only fairly marked intradermic reactions. Such a patient has a large number of highly sensitized areas in his skin which may possibly throw off antibodies into the blood. The beginning dose may in most cases be much higher without fear of reaction. Such a method would quickly lead to doses that cause response in the organism, and so bring about the formation of antibodies which occur more often with large than with small doses.

The rate of increase of the dose early interested me as I found that when I increased the dose by tenths of a cubic centimeter of the various dilutions (each of which is always ten times the strength of the preceding) I frequently obtained reactions when I increased from 1 to 2 or from 2 to 3 tenths. This led me to interpolate $1\frac{1}{2}$ and $2\frac{1}{2}$ tenths and to drop out 7 and 9. Later, with the aid of the late Mr. Pope, I constructed a logarithmic scale in which the increase was by geometrical proportion. This was based upon Fechner and Weber's law, namely, to increase the reaction in arithmetical proportion it is necessary to increase the stimulus in geometrical proportion. This table enables me to increase the dose from 0.01 to 1 c.c. of any dilution, using any rate of increase that I wish to select from 300 per cent. down to 12 per cent. I usually employ a rate of increase of 50 per cent. and find reactions no more likely to occur at one point of the scale than another.

The intervals are usually three or four days for the smaller doses and seven days for the larger doses.

The second method of giving tuberculin depends upon repeating the same dose at much longer intervals. Wright was the first to suggest such a method of treatment. I confess that I have never used the opsonic index method for it appeared to me from the start as impracticable. Good results have been reported by this method but Wright early stated that auto-inoculation was so frequent and so easily produced in pulmonary tuberculosis that his method was of little avail. On the other hand, Kinghorn and Twichell showed when an attempt was made to attain tuberculin tolerance, irrespective of the opsonic index, and the dose given in either the negative or the positive phase, the results were about the same. The opsonic index they concluded could be disregarded when tuberculin tolerance was aimed at. Many of us who have given tuberculin have, from time to time, received accidental inoculations which resulted in severe reactions. After recovering from such a reaction many experience a pronounced feeling of well being, which is so marked in some patients after the tuberculin test, that they have requested me to give them the tuberculin treatment. Such facts led W. C. White to attempt to estimate for each patient the dose of tuberculin that will just fall short of a fairly marked reaction. He makes use of the cutaneous

test and applies a definite quantity of tuberculin to an abrasion made so deep that the pink of the corium can be seen without producing any exudation of serum or blood. He then covers the tuberculin with a vaccination shield and allows it to dry *in situ*. When the cutaneous reaction at the end of the forty-eight hours has not exceeded 5 mm. he calls it the desired reaction and proceeds to give this dose, not subcutaneously, but in the lower layers of the skin where it causes a local or "Stichreaktion" of 20 to 40 mm. in diameter. If given oftener than every two weeks, he believes the patient acquires tolerance for tuberculin and so his interval is two weeks. I cannot subscribe to all the details of this method but in certain cases it is of apparent usefulness.

I shall not attempt to go into any details about increasing the dose when tuberculin tolerance is the aim. A good general rule is never to increase the dose when there has been any pronounced deviation from the usual trend of the disease. Another rule is when in doubt about giving an increased dose, do not do so. A very curious thing is that when tuberculin helps a patient very much, small doses appear to have as beneficial effects, certainly upon the symptoms, as larger. Tuberculin treatment, whatever working hypothesis is adopted, must be looked upon as a method of active immunization. Since this is the fact, it is useless to expect body cells, already flagging, to react with an adequate response. At such periods, tuberculin treatment should be omitted.

THE RESULTS. The goal of treatment in every patient is the cure of his disease or the alleviation of his symptoms. The estimation of the results of such treatment, however, is not always easy, for in many instances at least two personal equations enter, that of the patient and that of the physician. I am convinced that the explanation of the excellent results reported, for example, in pulmonary tuberculosis by the use of such substances as urea, sanosin, lignosulphite, griserin, nucleic acid, hetol, etc., are due far less to the action of the drug *per se* than to the effect of suggestion on the patient, perhaps unconsciously exerted, through the faith of the physicians who have first employed them. Certainly most of them when given as it were "in cold blood" produce such poor results that their use has been largely discontinued. Tuberculin cannot escape this weakness and indeed I believe its value can be greatly enhanced when the administrator has implicit faith in its curative properties and imparts that faith to his patients. The scientific physician of today who keeps faith with himself and refuses in such chronic and relapsing diseases as pulmonary tuberculosis to promise a "cure" to any patient by the use of any means, will certainly divest that means of a certain amount of suggestion and may rob it of some results that an absolute believer could impart to it. Such a believer, however, can get no idea how much of the results are due, for example, to tuberculin and how

much to the faith he has imparted to his patients. However, I am not here to discuss suggestion or auto-suggestion but the effect of tuberculin. I might say that the only suggestion I employ in connection with tuberculin is auto-suggestion by the patient. I try to be frank with him and tell him at the outset that tuberculin may help him and will not harm him if properly given, for of this I feel sure. One of my friends, whose faith in tuberculin is such that he can I believe honestly promise his patients that he will cure them with it, should get far better results than I, though he has never as yet collected his results.

Another factor which must be taken into account in discussing results of tuberculin treatment is the closer relationship that such treatment establishes between patient and physician. I must confess that I find it difficult to bring a patient to my office twice a week for months and discuss symptoms and fears, one of which gradually grows less while the other is often replaced by more or less indifference, borne of familiarity. When, however, I give this patient tuberculin, he and I can discuss his case in detail twice a week and I am able to discover slight but important changes in his condition, to check imprudence, and to change needless timidity into confidence in his ability to order aright his life. I cannot but believe that such a patient has a very great advantage over another who takes no such treatment. These factors must be taken into account in any treatment and I am convinced affect materially the results.

The Effect upon Symptoms. The symptomatic effect of tuberculin demands careful study and observation during treatment. Much work has been done upon the blood. It was early stated that tubercle bacilli were mobilized and occurred in the blood during the tuberculin reaction, but trustworthy evidence has never been produced that such is the case. The leukocytes show an essential increase, rarely over 10,000 per cubic millimeter and Arneth's neutrophilic picture may be shifted to the right and so approach nearer normal. In some instances, especially after large doses, agglutinins, precipitins, opsonins, and complement deviating substances occur in the serum. The urine may show a diazo reaction at the height of a general tuberculin reaction but does not do so otherwise. Some believe the quantity of urine is increased. The weight may decrease slightly after large doses and especially after reactions but when the course is finished the weight often increases rapidly. The appetite is usually unaffected except with reaction, but may be improved. The strength is quickly affected when the doses are too large. A feeling of discomfort, of ill-being, even malaise, may occur without rise of temperature. They indicate tuberculin poisoning and must be avoided. When the temperature varies from 99° to 100° F., following each dose it may be lowered or fall to normal. In other patients a slight temperature

of 99.5° F. becomes normal and remains so but in a few rises again when treatment is stopped. Rise of temperature may not occur until the patient is severely poisoned with tuberculin and must not be considered the sole guide to dosage.

The localizing symptoms may be increased or diminished according to the effect of the dose. The cough and expectoration may be lessened with each dose in such a way that the patient calls attention to it. Such a dose should always be repeated as long as such favorable results are obtained. In others the cough and expectoration increase with each dose and the treatment has to be abandoned. Usually there is no effect noticeable one way or the other. The virulence and morphology of the tubercle bacillus are apparently unaffected, but more patients taking tuberculin seem to lose their bacilli. This is especially true for the moderately advanced patients. Oppression in the chest is not uncommon, while pleurisy can rarely be attributed to tuberculin.

The physical signs may be increased, but it is more often difficult to detect during treatment any change in the physical signs other than what usually occurs from day to day in most patients.

My experience leads me to believe complications occur less frequently among patients receiving tuberculin treatment, but it does not exclude their occurrence.

The Untoward Results. Tuberculin, like arsenic or strychnine is a powerful poison which, when used injudiciously, is capable of great harm. The disrepute into which tuberculin fell at first was due to the selection of patients who should never have received it and to faulty dosage and too short intervals. Coincidence undoubtedly accounts in part for some of the so-called "unfortunate results." The mobilization of tubercle bacilli in the body, claimed by some to occur after tuberculin, has never been proved to occur either clinically or experimentally. In over 10,000 injections, 11 instances of hemoptysis more or less closely connected with or at least following tuberculin (in one to three days) have come under the writer's notice. In none was it severe, in most slight, and in 8 a previous hemoptysis had occurred. I have given, together with my assistants, to some 200 to 300 patients from 10,000 to 20,000 injections and have observed but two unhappy results at the site of inoculation. In one, a patient received too large a dose of bacillary emulsion at a single point and developed a sterile abscess which was healed by aspiration without opening. The second patient had what seemed to me to be a neuritis, as there was little to be seen at the site of inoculation. It was exceedingly painful and prostrating and deterred me for many years from injecting tuberculin into the arm. I might add that I now nearly always give it in the arm.

I have seen patients taking tuberculin do badly and have seen complications arise which might be attributed to it. I have also

seen the same complications occur in patients to whom we had thought of giving tuberculin. While I have tried to keep an open mind in regard to tuberculin, I may be somewhat prejudiced in its favor, though many of my colleagues in Saranac Lake would more readily believe the opposite. Consequently, when I say I have never seen any permanent untoward results to be attributed directly to tuberculin, I hope you will believe that I have tried to be fair.

There is some evidence, both experimental and clinical to show that tuberculin may cause nephritis, or at least, that it develops during treatment.

Experimental Results. The results of treatment of tuberculous animals with tuberculin has not been satisfactory. Life has been prolonged and changes have occurred in the lesions which demonstrate an attempt at healing but cure or bacterial immunity has not been effected. Some deny the value of animal experimentation in regard to tuberculin in man and much slipshod work has been published. Today the value of tuberculin treatment for man rests largely upon the results obtained in man.

Ultimate Results. The results in man have been for the most part good but many observers have failed to support their contentions with proof other than their personal belief or impressions.

Selection of patients certainly affects the results, and when only favorable cases with tubercle bacilli in the sputum are chosen, the results will be far better than when all patients are given the treatment. At the Adirondack Cottage Sanitarium we gave tuberculin to carefully selected patients for a time and then selected for a year or two the worst cases. Later we exercised no selection but allowed the patients to elect to take tuberculin treatment. We thought this would be the fairest test but in reality it has resulted in a selection against tuberculin as those patients who wished to stay a little longer because they were more advanced or ran a subacute course chose to take tuberculin. The patients we selected because they were the worst, did remarkably well. The results on the whole, when reduced to cold figures, with every error we could think of eliminated, showed that among the moderately advanced patients those who took tuberculin did better than those who did not, while for the incipient stage the difference was less pronounced. This held true for both immediate and ultimate results.

In the individual case, however, tuberculin often falls far short of what is hoped from its use. In early cases it is almost impossible to say how much good tuberculin does. In the more advanced cases favorable results are more often seen and in the very chronic cases the effect of tuberculin is in a few truly astonishing, so good, in fact, that no one questions it. It is these results that win for tuberculin its advocates and I am sure that after two or three

such cases few would doubt its efficacy in some patients. When, however, results are tabulated and impartial statistical methods applied, they are so far from upholding the impressions created by these few cases that the statistical methods themselves, and not the results of tuberculin, are questioned.

My observation leads me to believe that incipient cases treated with tuberculin do somewhat better than those not so treated, while the moderately advanced cases do much better. The ultimate results do not show such marked differences, but indicate that the treated, both incipient and moderately advanced, do better.

REST VERSUS CLIMATE IN THE TREATMENT OF PULMONARY TUBERCULOSIS.[1]

By William C. Voorsanger, M.D.,

VISITING PHYSICIAN TO MOUNT ZION HOSPITAL; CLINICIAN TO SAN FRANCISCO TUBERCULOSIS CLINIC, SAN FRANCISCO, CALIFORNIA.

The world is still knocking at the door of the medical profession asking for a cure for its greatest scourge, and we who are particularly interested in the treatment of pulmonary tuberculosis are certainly anxious to unite upon some sane rational therapy pending the discovery of a true specific.

Phthisiotherapists agree upon but one point, namely, that tuberculosis is curable. Their mode of procedure in effecting this cure varies to a considerable degree. As an example of this, two years ago I was able to collect 75 varieties of tuberculin in the market, each with its champions and devotees, claiming some particular merit for their special brand, seemingly forgetful of the fact that tuberculin is a product of the tubercle bacillus, call it by what name you will, and that success in treatment depends not so much upon the form used as upon its dosage and mode of administration.

So has it been with other measures for the treatment of tuberculosis as its therapy has evolved through the centuries from Hippocrates and Aretaeus, who knew little about it, down to Robert Koch, who has given us our present-day conception of the disease. Climatic treatment ruled supreme for many years, and particularly in the United States. It became the rule when a patient was pronounced tuberculous to send him to another climate—warmer, drier, higher, or lower—than his own. Colorado, California, Arizona, and New Mexico became the favored resorts, the four

[1] Read at the Seventh International Tuberculosis Congress held at Rome, April 14 to 20, 1912.

Meccas to whose shrines thousands of misdirected tuberculous individuals have gone, the major portion of whom never returned.

In the majority of cases the doctor is responsible for sending his patient away from home, either from a belief that another climate will benefit him or because (which unfortunately is too often the case) his own therapeutic resources are at an end and he wishes to put the responsibility of the death of his patient upon someone else. I wish to state emphatically that I consider it criminal to send an advanced case of tuberculosis away from home under the delusion that another climate will cure him. Any physician of the Pacific Coast, and particularly we in California, can bear testimony to having seen innumerable cases of advanced tuberculosis, sent by their physicians, for whom absolutely nothing could be done. Let us once for all put every personal or material consideration aside and come out boldly for this principle: That climate *per se* plays but a very small role in the present-day treatment of pulmonary tuberculosis. Most of us believe this, some still doubt, some still have faith in the high altitude treatment, some in the dry air climate, some in a change from any climate to any climate.

I can readily understand that a climate which has a maximum amount of sunshiny days in the year will prove more cheerful to a patient than one where it constantly rains. Upon this ground alone can I see much merit in change of climate. Where a patient is depressed and firmly convinced that he cannot get well a change of scene and a brightening of his surroundings may become important. But the unqualified transference of tuberculars from one climate to another without individualization is bad therapeutics.

We see more tuberculosis in California than in any part of the United States with the possible exception of Colorado, which proves that physicians do not yet recognize the truth that climate unaided never did and never will cure tuberculosis. A considerable proportion of the fairly advanced cases, which I see in both clinical and private practice is composed of patients who have been to one or more sanatoria for a cure. This certainly must be the experience of other physicians in California interested in tuberculosis and goes to prove that the tubercular who cannot be cured at home cannot be cured elsewhere, other things being equal. Why do we still constantly persist in the blunder of making a fetish of climate, imbuing the mind of the sufferer with its almost supernatural influence, and as a result causing him to live uncontrolled and unadvised, always getting worse but believing the contrary? To remedy this error medical men must be convinced that tuberculosis, particularly the pulmonary form, is a disease of metabolism, a disease of cell destruction, a disease of tissue waste, a disease where bacteria are locked up in bronchioles, generating toxins, and that our only chance of arresting this devastation is to stimulate the natural defences within the body, the antibodies. Climate cannot

do this. All the grand results attributed to climate in the past have been due to open air, food, and the control within a sanatorium. Air is air whether high or low, and can be obtained in any climate. The open air and sanatorium treatment must be distinctly differentiated from so-called climatic treatment. If you send cases to a distinct locality for the purpose of getting care, proper medical attention, and better facilities than can be obtained at home no fault can be found. But the physician first and the patient secondly must learn that in treating pulmonary tuberculosis we are attempting to stop waste; we are attempting to check toxemia; we are striving to put the body in such condition that the introduction of artifical toxins will stimulate its natural defences and form a maximum amount of antibodies. Only in this way do I believe we will be able to create out of the experience of the past a rational tuberculosis therapy.

At the last Tuberculosis Congress, Williams, of London, covered these points most ably by stating "that the history of consumption has ever shown that more has been accomplished by measures which augment and reinvigorate the resisting powers of the sufferer than by measures which aim at destroying or rendering harmless the invading tubercle bacillus."

Sewall, of Denver, in a recent article on open air, concluded that there was no existing proof that the increase of carbon dioxide, the decrease of oxygen, or the addition of organic animal matter under ordinary circumstances could prove deleterious to health. Air cannot destroy the effects of the tubercle bacillus primarily. Air simply does its share in stimulating metabolic change.

Osler has said that a man with beginning tuberculosis may fight a winning battle if he lives out of doors in any climate whether high, dry, cold, low, moist, or warm.

What then becomes our duty in the treatment of a curable case of pulmonary tuberculosis? As I see it after struggling with the problem for several years, tempering personal experience and failure with the experience and failures of others, it is plainly to build up a faulty metobolism and if possible produce an immunization. For my own guidance I have tabulated tuberculosis therapy as follows, each heading in its relative degree of importance: (1) Rest; (2) diet; (3) open air; (4) tuberculin therapy; (5) climate.

I am firmly convinced and shall try and prove my position by the record of results which are given later that rest is our most important therapeutic agent in the treatment of pulmonary tuberculosis. Brehmer was the first to introduce a system of graduated exercise into the treatment of tuberculosis. His work has been augmented and improved upon by Paterson at the Brompton Sanatorium, Frimley. Latham also in treating his patients insists upon rest and graded exercise as the best therapeutic agent for reducing fever and toxemia and controlling the danger of autoinoculation.

We all recognize the value of open air for twenty-four hours daily if possible. We sanction caloric feeding, which means not overfeeding, not forcing the organism to assimilate beyond its power, but sufficient feeding to restore body-weight to normal. In a particular individual most of us believe in tuberculin therapy, the conviction gradually becoming fixed that it will some day become a true specific, but we are not all ready to accept the doctrine of the importance of rest applied scientifically. Formerly a patient was told "to go west and rough it." For this reason the physician on the western coast of the United States has been able to see so many cases of tuberculosis. Those who come west and rough it uncontrolled seldom get well. Often, too, we see the arrested case breaking down through overstrain.

Rest means freedom both from physical and mental strain. Rest should be applied in fairly accurate dosage just as we figure out diet in calories and our tuberculin in milligrams. It is not sufficient to tell the patient to take plenty of rest and not to walk too much, and not to engage in mental worry or work. The number of hours of rest *per diem* should be prescribed, and if mental strain is present the doctor should acquire the patient's confidence, learn its nature, and if possible remove it.

Again, the importance of graduated rest and exercise in administering tuberculin cannot be too strongly dwelt upon. Tuberculin reactions, failure to acquire arrest or retrogression of a tuberculous process may often be attributed to our forgetting that autoinoculation goes on continually within the body of the tubercular, that tuberculin itself is being produced, and that antibodies are being generated. If we are ever to obtain an immunity in tuberculosis it can only be by creating a proper balance, that is, by administering the toxin (tuberculin) for the purpose of supporting and stimulating the natural defences already in the body, the antibodies. Any scientific theory which has been developed, whether the Arloing and Courmont agglutinin theory, the Bordet and Gengou antibody theory, or the antituberculin hypothesis of Wassermann and Bruck, cannot overcome the truth that tuberculin can only become the true specific of the future if we realize that we do not inject antibodies, but stimulate those already in the body.

Following the experience of Nathan Raw,[2] with bovine T. R. I began injecting my cases with bovine tuberculin, and in October, 1910, reported[3] 28 cases, of which 15 were apparently cured or arrested. I consider this result most satisfactory and attributed it to the greater efficacy of the bovine tuberculin over the human form in the treatment of pulmonary tuberculosis.

I have continued in the exclusive use of this form of tuberculin and can now report 210 cases in which the results have practically

[2] Lancet, February 10, 1908.

[3] California State Jour. Med.

been as good as in the original 28. But I have changed my viewpoint somewhat, and although still believing that bovine tuberculin is the toxin of choice in the treatment of tuberculosis caused by Bacillus typus humanus, I must attribute my results primarily to the enforced rest to which all my patients are subject. We err if we do not appreciate that tuberculosis with fever is like any other disease with fever, the result of bacillemia and toxemia and should be treated with rest in bed, that tuberculosis with emaciation is like any other devastating process and needs rest; that tuberculosis with weakness is like myocardial weakness and needs rest if we are to acquire proper functional restitution.

In order to prove the assertion that rest is the most important agent in our therapeutic armament for fighting tuberculosis, I have procured records from most of the large sanatoria upon the Pacific Coast and in Colorado, in order to compare them with my own results obtained in San Francisco. The directors of the various sanatoria were written to and the results as herein given (see Table on p. 540) are taken from their personal statements.

In a comparison of the results obtained by various observers in their respective localities as shown in the following table some facts stand out rather prominently. The greatest percentage of apparent cures has been obtained by the Pottenger Sanatorium and the National Jewish Hospital at Denver; the greatest percentage of arrests by the Colfax School for the Tuberculous; the Barlow Sanatorium at Los Angeles, and myself; the greatest number of improvements by the Walter Henry Memorial Sanatorium at Seattle and the United States Naval Hospital at Las Animas, Colorado, and the United States Army Hospital at Fort Bayard, New Mexico. The altitude of the two last named sanatoria are respectively 3800 and 6100 feet and the absence of successful result (cures and arrests) is accounted for by the fact that most of the cases at Fort Bayard are chronic, being discharged tuberculars from the United States army, and a great many sent to Las Animas are advanced. The two sanatoria are situated in regions once thought to possess absolute curative climatic power, and the altitude of Fort Bayard is the highest of any locality mentioned in the table with the exception of Fort Stanton. This should prove sufficiently that climate cannot influence materially a tuberculous process and that a tuberculous patient who cannot get an arrest at home cannot obtain it elsewhere.

The Pottenger Sanatorium, situated at a comparatively low altitude (1000 feet) above sea level and with a wide range of temperature, shows the best results. Dr. Pottenger does not attribute his success to climate but to "all measures which aid in building up and nourishing the body, such as open air; good food; the careful adaptation of rest and exercise; suitable baths and medicinal tonics; to the end that the cells will be as responsive as possible; then furnishing the toxin necessary to stimulate the cells to the

Place.	Altitude. Feet.	Range of temperature.	Capacity of bed.	No of cases 1910–1911.	Apparently cured. Per cent.	Disease arrested. Per cent.	Improved. Per cent.	Unimproved. Per cent.	Died. Per cent.
Barlow Sanatorium, Los Angeles, Cal.	330	94° to 30° F.	40	59	9 (15.59)	21 (35.59)	11 (18.64)	10 (16.95)	8 (13.56)
Pottenger Sanatorium, Monrovia, Cal.	1000	109° to 31° F.	100	About 200	Beginning cases 80 Advanced 30 Average 55		Not given	Not given	Not given
United States Army Hospital, Fort Bayard, New Mexico	6100	102° to 30° F. below zero	400	435	12 (2.76)	17 (3.91)	178 (40.7)	177 (40.7)	50 (11.7)
United States Army Hospital, Fort Stanton, New Mexico	6200	83° to 21° F.	250	144	23 (16.00)	26 (18.00)	23 (16.0)	28 (19.4)	41 (28.4)
United States Naval Hospital, Las Animas, Colorado	3800	103° to 20° F. below zero	238	213	28 (13.10)	20 (9.40)	82 (38.5)	50 (23.4)	33 (15.5)
Union Printers' Home, Colorado Springs, Colorado	6035	94° to 15° F. below zero	54	34	6 (17.60)	9 (26.10)	11 (32.3)	8 (23.5)	
National Jewish Hospital, Denver, Colorado	5280	100° to 29° F. below zero	130	224	52 (23.20)	49 (21.80)	33 (14.7)	79 (31.2)	7 (3.1)
Colfax School for the Tuberculous Colfax, Cal.	2420	107.5° to 32° F.	50	128	6 (4.70)	39 (30.40)	35 (27.5)	40 (31.2)	8 (6.2)
Maricopa Hospital, Arizona . .	1200	118° to 28° F.	25	99	.....	5 (5.50)	5 (5.5)	15 (16.5)	64 (64.1)
Walter Henry Memorial Sanatorium, Seattle, Wash.	300	86° to 22° F.	31	48	1 (2.10)	2 (4.20)	22 (45.8)	13 (27.0)	10 (21.0)
San Francisco (Author) . . .	18	49.2° to 87° F.	..	1909–1911 210	31 (14.70)	74 (35.20)	34 (16.2)	36 (17.1)	35 (16.7)

[4] Dr. Pottenger would not segregate his cases, stating that he averaged about 80 per cent. of cures and arrests in beginning cases and about 30 per cent. in advanced cases. This would make an average of 55 per cent. apparent cures and arrests.

production of protective substances as is done by intelligently employing tuberculin." He also lays great stress upon individualization, stating that "no physician can obtain the best results unless he can see something beyond tuberculosis and recognize the fact that tuberculous patients are drawn from the mass of human beings, hence liable to all the ills of un-tuberculous individuals."

Dr. M. Collins, in charge of the National Jewish Hospital for Consumptives at Denver, states: "I consider results obtained to a large degree due to our climatic conditions as well as to the *care, discipline*, and *attention* which our patients receive in the hospital itself." His apparent cures were 23.2 per cent.; arrests, 21.8 per cent. At Fort Stanton, New Mexico (United States Army Hospital), Dr. F. Smith in charge states that various degrees of importance are attached to the climate of this particular locality by different men. Fort Stanton shows 16 per cent. of apparent cures and 18 per cent. of arrests, while Fort Bayard for chronic cases in practically the same locality shows only 2.7 per cent cures and 3.9 per cent arrests. Dr. Smith in a recent publication states "sometimes a change is either unnecessary or useless, and moreover a climate adapted to the needs of one individual may be wholly unsuited to those of another." The Barlow Sanatorium, which shows apparent cures 15.25 per cent. and arrests 35.59 per cent. through its superintendent, Dr. R. L. Cunningham, makes this statement; "I do not consider this locality as favorable as certain places in Arizona or New Mexico and even some points of California on the desert," and still the Barlow Sanatorium shows better results than the Maricopa Hospital in Arizona, the Fort Stanton Hospital in New Mexico, or the Peers School for the Tuberculous at Colfax.

Dr. Peers, of Colfax, a careful observer, attributes his results to change of climate, freedom from fog and contaminating organization, and ability to live the outdoor life without discomfort 365 days in the year.

Now, to compare the above results with my own in 210 cases, treated at practically sea level, some in a sanatorium but the majority at home, ambulant. Before doing so I wish to make one observation: A just comparison can only be made if apparent cures and arrests are grouped, because we naturally all have different ways of construing results and what one dubs an apparent cure another may call an arrest. Personally, I am careful how I list a case as cured, since many of my cases which at the end of treatment were symptomless have relapsed in from six months to one year. I have also treated many cases which have been discharged from various sanatoria as cured. We all know the inaccuracy of statistics, and only by following our cases can our reports be exact. All the cases here reported have been under observation at least three years, and with but few exceptions their conditions at the present time are known. In the attempt, therefore, to be as conservative as possible,

I can report of 210 cases, apparently cured, 14.7 per cent.; arrested, 35.2 per cent.; total, 49.9 per cent., practically a 50 per cent. successful result in a series in which the cases were not selective but taken at random from all classes of people. Tabulating together apparent cures and arrests from the various places under discussion we have: Barlow Sanatorium, 50.8 per cent.; Pottenger Sanatorium, 55 per cent.; United States Army Hospital at Fort Bayard, 6.67 per cent.; United States Army Hospital at Fort Stanton, 34 per cent.; United States Army Hospital at Las Animas, 22.5 per cent.; Union Printers' Home, Col. Springs, Col., 43.23 per cent.; National Jewish Hospital, Denver, Col., 45 per cent.; Colfax School for the Tuberculous, Cal., 35.1 per cent.; Maricopa Hospital, Arizona, 5.5 per cent.; Walter Henry Memorial Sanatorium, Seattle, Wash., 6.3 per cent.; Author (San Francisco), 49.9 per cent.

A survey of this grouping will show that my results are practically as good as those obtained at other places despite the fact that the climate of San Francisco has always been regarded as impossible for the cure of tuberculosis. To be sure, the net result in any report of cases will depend largely upon the number of advanced cases handled, but I feel certain that my present series contains as many advanced cases as the majority of sanatoria in the statistical table. This is demonstrated by a death rate in the series of 16.7 per cent., with no improvement in 17.1 per cent.

I am convinced that climate today plays the least important role of any of our therapeutic aids to the treatment of pulmonary tuberculosis. The fact is becoming more and more evident that the war against tuberculosis must be waged by each community within its own borders and not as heretofore each community shirking responsibility by making some other its dumping ground. Relapses are most common in patients who have received a cure in one climate and who attempt to live in another. Consequently, a tubercular should live in the climate in which he has been cured which must naturally be his home climate.

We must not deceive ourselves in believing that the therapeutic millenium of tuberculosis has arrived, and that we can absolutely cure it. We none of us know how many of our cures or arrests will stand the test of time.

In conclusion, this much I want to set forth with positiveness. If climate shall in future be disregarded and communities develop phthisiotherapists who in their own climate will build up a faulty metabolism of their patients through rest, open air, and proper feeding in order to, with the aid of tuberculin, stimulate the generation of antibodies within the body, a long step forward will have made in the therapy of tuberculosis.

I wish to express my thanks to the various directors and superintendents of the sanatoria and institutions above mentioned who have so willingly and kindly assisted me in making this report possible.

DIABETES MELLITUS AND TUBERCULOSIS.

By Charles M. Montgomery, M.D.,

INSTRUCTOR IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; PHYSICIAN TO THE HENRY PHIPPS INSTITUTE, UNIVERSITY OF PENNSYLVANIA, AND THE WHITE HAVEN SANATORIUM.

The association of diabetes mellitus and tuberculosis has been the subject of unusual interest during the last half-century. Richard Morton's[1] cases of diabetes associated with wasting (tabes) described in the seventeenth century were not cases of tuberculosis judging from the description of the cases. John Rollo,[2] in his book on diabetes, published in 1798, manifests no special interest in this subject, though he gives the clinical and postmortem records of a case of diabetes evidently complicated by pulmonary tuberculosis with cavity formation. The credit for the first report of a large number of diabetic cases, with special reference to tuberculosis of the lungs, belongs to Griesinger (1859), who records 250 cases. Windle, in 1883, reported the autopsies of 333 diabetic patients, with mention of the pulmonary conditions. Following Koch's discovery, in 1882 (see authorities cited by H. Fink[3]), tubercle bacilli were found in the sputum and lungs of diabetic patients (1883), and tuberculosis was produced in animals by inoculation with the sputum. Tuberculosis complicating diabetes has even been found in animals. Schindelka[4] reported pulmonary tuberculosis in a diabetic dog, and Berenger-Férand observed cerebral tuberculosis in a monkey. The interest in the two diseases has largely been directed toward the frequency of tuberculosis in diabetes and the various causes supposed to explain this frequent complication.

Analogies between Tuberculosis and Diabetes. A number of authors have been impressed with certain points of similarity between tuberculosis and diabetes. Thus Sauvage[5] speaks of the interference with nutrition in the two diseases, the abundant elimination of waste products in the urine, both organic and mineral, and the diminished respiratory activity. Shively[6] points to the progressive course in both diseases, to the emaciation, to the great fatality in early life, and the better resistance in later life, to the strong racial affinities, to their greater prevalence in cities than in the country, and to various other conditions common to both tuberculosis and diabetes. Purdy[7] states that the "terri-

[1] Phthisiologia, 1694. English translation.
[2] Cases of the Diabetes Mellitus, London, 1798.
[3] Münch. med. Woch., 1887, No. 37.
[4] Cited by B. Naunyn Der Diabetes Mellitus, 1906, p. 152.
[5] Paris Theses, 1895.
[6] New York Medical Journal, May 16, 1908, p. 933.
[7] Diabetes Mellitus, 1890. p. 14.

tories furnishing the highest mortality from diabetes in the United States coincide very closely with those furnishing the highest mortality from consumption. The very frequent termination of diabetes in consumption lends significance to this fact."

Diabetes and Tubercular Heredity. A few writers have been impressed with the frequency of a family history of tuberculosis in diabetic patients. Thus, Croner[8] relates the occurrence of an hereditary or family tendency to tuberculosis in 37 out of 100 diabetics, 12 more of whom were themselves tubercular. He cites Schmidt, who believes there is a diabetic predisposition or diathesis in tuberculous families. Among 48 cases of diabetes collected by the writer only 2 had recorded a definite tubercular family history, and 6 more a questionable family history of tuberculosis, but the completeness of these records in regard to family history cannot be vouched for. Even Croner's figures are not especially remarkable when compared with the great prevalence of tuberculosis.

Glucose as an Etiological Factor in Predisposing Diabetic Patients to Tuberculosis. The assumed predisposition of diabetics toward infection with the tubercle bacillus has been explained most frequently on the hypothesis that glucose outside of the body exerts an especially favorable influence on the growth of these organisms. Glucose added to a number of culture media, for example blood serum and bouillon, exerts as favorable or nearly as favorable an influence on the growth of tubercle bacilli as does the more commonly used material, gelatin (Eastwood[9]). In comparison to blood serum, however, glucose, whether added to blood serum or other media, never has an influence on the development of tubercle bacilli greatly beyond that of blood serum alone, and toward some strains of the tubercle bacillus has an even less favorable influence than the normal blood serum. Whatever especially favorable action has been found for the action of glucose has been the result of using glucose in strengths of 5 per cent. or more, while in the blood of diabetic patients the amount rarely reaches 1 per cent.—a proportion attained by only one patient in the literature[10] reviewed by the writer. Handmann's[11] experiments are the only ones I have found in which small quantities of glucose (0.5 to 1 per cent.) were added to normal blood. He states that this amount of glucose does not render it any better culture medium for staphylococci, nor does it lower the bactericidal action toward these organisms, and does not lessen the normal opsonin in the blood serum. There is equally little evidence to support Honl's[12] claim that the growth

[8] Deutsch. med. Woch., 1903, xxix, 821.

[9] Second Interim Report, Royal Commission on Human and Animal Tuberculosis, London, 1907, Part II, Appendix, vol. iv.

[10] B. Naunyn, Der Diabetes Mellitus, 1906, p. 188.

[11] Deutsch. Archiv f. klin. Med., 1911, cii, 1.

[12] Wien. klin. Rundschau, 1898, xii, 245, 265, 299.

of the organisms of mixed infections is promoted by the glucose in sufferers from diabetes. The animal experiments of Budjwid,[13] in which he injected dogs hypodermically with suspensions of bacteria in 12 to 25 per cent. glucose solutions, and of Preyss[14] and Leo,[15] who investigated the development of tuberculosis in animals rendered glycosuric through phloridzin, shed no light on the subject. Some writers (see C. von Noorden[16]) believe that the high glucose content of the blood in diabetes results in injuries to the tissues that predispose them to infection.

Bernheim and Dieupart[17] make an interesting report on tuberculosis in the working people of a certain sugar factory. In a dispensary in the neighborhood of the factory 150 cases of tuberculosis were observed among 1500 employees, women being affected more frequently than men. The writers attribute the great frequency of the disease less to the chemical influence of the sugar than to the mechanical injury to the bronchial mucous membrane produced by the sharp sugar dust. Most of the employees in the sugar factory showed serious injuries to the teeth. The writers state that exactly as in the case of diabetes, tuberculosis with the working people of the sugar factory takes a rapid course, and is always fatal.

Loss of Weight. Loss of weight either on its own account or because of various conditions causing it is often stated to predispose the individual to tuberculosis, and particularly the diabetic patient in whom the wasting may be extreme. Simple lack of nourishment is commonly considered to favor the development of tuberculosis, but as it is apt to be associated with poor surroundings and unusual opportunities for exposure to the tubercle bacillus, infection cannot be excluded as the chief or only cause of the disease in many of these poorly nourished persons. Among non-tuberculous persons of subnormal weight living under better conditions there is no positive demonstration that tuberculosis develops with unusual frequency. Experimental work on animals has shed little light on the effect of insufficient feeding as a cause for tuberculosis, most of the experiments failing to exclude all abnormal factors except the reduced diet. Preyss[18] noted no appreciable effect on the development of tuberculosis in underfed animals. In many chronic affections accompanied by loss of weight, there is no special tendency for the development of tuberculosis, for example, pernicious anemia (Cabot[19]), leukemia (Osler), exophthalmic goitre (Dock),[20] and various malignant diseases. Among wasting diseases having tuberculosis as a fre-

[13] Centralbl. f. Bakteriologie u. Parasitenkunde, 1888, iv, 577.
[14] Münch. med Woch., 1891, xxxviii, 418.
[15] Zeitschr. f. Hygiene, 1889, vii, 505.
[16] Die Zuckerkrankheit, 1910, p. 165.
[17] Tuberculosis, Berlin, 1908, vii, 194.
[18] Münch. med. Woch., 1891, xxxviii, 418.
[19] Osler's Modern Medicine, iv, 625.
[20] Ibid., vi, 377.

quent complication, cirrhosis of the liver has been especially emphasized by Osler[21] and Kelly,[22] and others, but the mortality from tuberculosis complicating cirrhosis of the liver does not appear particularly remarkable when compared to the general tuberculosis mortality.

Miscellaneous Etiology. Of the many other causes offered to explain the alleged hypersusceptibility of diabetic patients to tuberculosis, only a few will receive passing mention. Thus "diminished vigor," "lessened resistance," "metabolic disturbances with excessive elimination and deficient absorption interfering with nutrition" (Sauvage), the presence in the body of various poisonous substances, atrophy and inflammation of the respiratory passages (Blumenfeld[23]), and various other conditions are supposed to favor the development of tuberculosis in diabetics. However, neither the facts nor the reasoning furnished in support of these alleged causes are convincing, and most of the explanations are little more than plausible, being often the result of *post hoc, propter hoc* reasoning, whereby the frequency of tuberculosis in diabetes is explained by the various abnormal conditions associated with diabetes.

Evidences Indicating a Particularly Acute Process in Tuberculosis Complicating Diabetes. In support of the idea that diabetes predisposes to tuberculosis, it has been urged that the tuberculosis often pursues a very brief course in diabetes and at autopsy frequently reveals an acute process. West[24] mentions 50 diabetic cases studied post mortem in which 21 were tuberculous, 4 of these presenting the lesions of chronic tuberculosis, while in the rest phthisis was active and the cause of death. Dreschfeld[25] speaks of an acute tuberculous broncho-pneumonia occurring in diabetes, running a more rapid course than ordinary phthisis, and being characterized by an early and very extensive formation of cavities. Babcock[26] likewise supports this view. Undoubtedly tuberculosis is one form of terminal infection that frequently attacks the diabetic. Out of 355 autopsies on diabetic cases collected from the literature and postmortem records, 138 showed pulmonary tuberculosis, mostly acute. This subject is dealt with further under Clinical and Pathological Aspects of Tuberculosis in Diabetes

Hematological Studies Relating to Etiology. Particularly interesting are the results of Da Costa and Beardsley,[27] who found in diabetics a lowered opsonic index toward the Staphylococcus pyogenes, the Streptococcus pyogenes, and the tubercle bacillus.

[21] Practice of Medicine, 1896, p. 476.
[22] Osler's Modern Medicine, v, 779.
[23] Therap. Monatshefte, February, 1899.
[24] Diseases of the Organs of Respiration, 1902, ii, 523.
[25] Medical Chronicle, Manchester, 1884-85, i, 5.
[26] Diseases of the Lungs, p. 197.
[27] Amer. Jour. Med. Sci., September, 1908.

Studies on the resisting powers of the blood have also been carried on in depancreatized dogs. Sweet[28] found that after removal of the pancreas in dogs there was a complete loss of bactericidal power in the blood toward B. coli communis, B. typhi abdominalis, and B. dysenteriæ. Thomas and MacPhail,[29] found that the opsonic index curves for Micrococcus aureus regularly declined in all depancreatized dogs. Nebelthau,[30] on the other hand, found no differences in the development of tuberculosis in depancreatized and control dogs. But in the experiments with depancreatized dogs the interval until the time of their death was always too short, never over six and usually within three weeks, to make a fair comparison between occurrences in these animals and in human beings the subjects of diabetes.

Raw[31] has conducted some suggestive experiments, too few to carry weight, to show the effect on the growth of the tubercle bacillus on artificial media through the addition of blood from a diabetic patient.

Frequency of Tuberculosis in Diabetes. The frequency of tuberculosis as a complication of diabetes has greatly impressed nearly all writers on this subject except von Noorden and Cornet, it being apparently assumed that this frequency considerably exceeds the general tuberculosis mortality. This conclusion, doubtless, largely results from using general hospital statistics like those of Adami and McCrae,[32] who found only 17.3 per cent. of tuberculous cases (after excluding all healed and latent cases) in 1000 autopsies, and from failure to use figures expressing the general tuberculosis mortality. Thus, one-third of all deaths in persons aged between fifteen and forty-four years, according to Baldwin,[33] are due to tuberculosis. Cornet's[34] figures for Prussia in the decade 1881 to 1890 show that between the ages of fifteen and sixty years the tuberculosis mortality varied according to age and sex between 25.1 and 46.6 per cent. According to the United States Census Report for 1909 the number of deaths from tuberculosis of all forms "per 100 deaths from all known causes at each age" in the registration area was as follows:

Age . .	Under 10	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	Over 90
Per cent.	3.4	26.1	37.0	29.3	18.6	10.4	5.3	2.5	1.0	0.0

Conclusions, moreover, are unreliable if based on figures obtained previous to the discovery of the tubercle bacillus; for instance, the figures of Griesinger (1859), who in 250 diabetics

[28] Jour. Med. Research, 1903–4, v, 255.
[29] Monthly Cyclopedia and Medical Bulletin, September, 1911, p. 535.
[30] Arch. f. exper. Path. u. Pharmak., 1901, xlix, 384.
[31] Tuberculosis, Berlin, May, 1911.
[32] Sixth International Congress on Tuberculosis, v. I, pt. I, 325.
[33] Osler's Modern Medicine, iii, 143.
[34] Tuberculosis, 1904, p. 277.

states that tuberculosis occurred in 42 per cent. of the cases and was the cause of death in 39 per cent. Bouchardat (1875) claims to have found tuberculosis in all of 19 autopsies on diabetic patients, and Windle[35] found that more than one-half of 333 autopsies on diabetic subjects "presented the changes of the disease or group of diseases known as phthisis." Among other points affecting the reported frequency of tuberculosis in diabetes are the stage and degree of activity and the accuracy of diagnosis of the tuberculosis, the age of the patients, and the stage of the diabetes.

Frequency of Tuberculosis in Diabetes. Cases of Diabetes Non-fatal while under Observation: Writer's collected cases, 51; tuberculous, 0. Philadelphia Polyclinic Hospital Dispensary (Dr. Riesman), 10 cases; tuberculous, 0.

Cases of Diabetes in Which Mortality is Generally not Mentioned: R. T. Williamson,[36] 100 consecutive cases; tuberculous, 29 (14, signs of advanced phthisis; 14, slight signs at apices; 1, detected post mortem). Da Costa and Beardsley,[37] 50 cases; tuberculous, 10. W. Croner,[38] 100 cases; tuberculous, 12. F. M. Sanwith,[39] in Egypt, number of cases not mentioned; tuberculous, about 12 per cent. B. Naunyn,[40] 149 "pure" diabetic cases; tuberculous, 25. B. Naunyn, 103 diabetic cases resulting from demonstrable organic diseases; tuberculous, 8. N. Raw,[41] 62 diabetic cases, with 27 autopsies; tuberculous, 37 (2, abdominal tuberculosis).

Fatal Cases: (Autopsies not performed or not mentioned.) Writer's collected cases, 35 (none autopsied), pulmonary tuberculosis, 3. F. T. Frerichs,[42] 250 cases; pulmonary tuberculosis, 34.[43] C. von Noorden[44] (private cases), 292; tuberculous, 15 (pulmonary, 14; intestinal, 1). R. T. Williamson,[45] 42 cases; pulmonary tuberculosis, 6. R. M. Fitz[46] and E. P. Joslin, 20 cases; pulmonary tuberculosis, 3.

Cases Autopsied: Writer's collected cases, 25; pulmonary tuberculosis, 6; all active. F. T. Frerichs,[47] 55 cases; pulmonary tuberculosis, 21. I. Honl,[48] 29 cases; pulmonary tuberculosis, 12. H. Noltemius,[49] 20 cases; pulmonary tuberculosis, 4; all active. B. Naunyn,[50] 50 cases; pulmonary tuberculosis, 20; exclusive of old

[35] Dublin Jour. Med. Sci., 1883, lxxvi, 112.
[36] Diabetes Mellitus, 1898.
[37] Loc. cit.
[38] Deutsch. med. Woch., 1903, xxix, 821.
[39] British. Med. Jour., October, 1907, p. 1059.
[40] Loc. cit.
[41] Loc. cit.
[42] Ueber den Diabetes, 1884, p. 132.
[43] W. Fox (Diseases of the Lungs and Pleura, 1891, p. 551) and S. West (Diseases of the Organs of Respiration, 1902, ii, 523) wrongly quote Frerichs as recording 87 tuberculous cases among 250 diabetics.
[44] Loc. cit.
[45] Loc. cit.
[46] Jour. Amer. Med. Assoc., July 23, 1898, vol. xxxi.
[47] Loc. cit.
[48] Wien. klin. Rundschau, 1898, xii, 245, 265, 299.
[49] Beitrag zur Statistik u. pathologischen Anatomie des Diabetes Mellitus, Kiel, 1888.
[50] Loc. cit.

scars. S. West,[51] 50 cases; pulmonary tuberculosis, 21; (4 chronic, remainder active and cause of death). Reports of the Surgeon-General 1895-1905, 5 cases; pulmonary tuberculosis, 2. K. A. Heiberg,[52] 5 cases; pulmonary tuberculosis, 0. R. T. Williamson,[53] 24 cases; pulmonary tuberculosis, 12. J. Seegen,[54] 92 cases; pulmonary tuberculosis, 40. Total, 355 cases; pulmonary tuberculosis, 138 (38.9 per cent.).

Cases of Diabetes Showing Effect of Different Living Conditions: Dr. David Riesman, diabetic cases in private practice, 45; tuberculous, 1. C. von Noorden,[55] diabetic cases in private practice, number not mentioned; tuberculous, 5.5 per cent. Diabetic cases in public hospitals, number not mentioned; tuberculous, 15.1 per cent. Diabetic cases in Russian Jews, 45; tuberculous, 27 (60 per cent.).

The above tabulation illustrates well the frequency of tuberculosis in diabetes under a number of conditions. The tabulation with the autopsy figures gives the most reliable information, if it is borne in mind that these are probably all or nearly all hospital cases. The clinical cases vary in part with the carefulness and diagnostic skill of the physicians in charge. Thus, compare the writer's collected fatal but non-autopsied cases with those examined post mortem. Carelessness in diagnosis is particularly well illustrated by a febrile patient under constant and in many respects careful observation in a hospital for over eight months without there being found any abnormal condition in the lungs until the autopsy revealed extensive bilateral tuberculosis. The table on the effect of different living conditions is very instructive.

Frequency of Tuberculosis in Diabetes According to Age. Available figures on the incidence of tuberculosis in diabetes according to age are unfortunately very meagre and do not demonstrate conclusively any variation in diabetics from non-diabetics. In children and old people tuberculosis is to be less frequently expected than in those of the intervening period. Sauvage[56] refers to 7 cases of tuberculosis in 42 diabetic infants. Wilcox[57] cites a number of authors who consider tuberculosis among the most frequent complications of diabetes in infants and young children, an opinion apparently not endorsed by Holt.[58] Williamson[59] believes that young patients who do not die at a comparatively early stage from coma or some intercurrent disease usually develop tuberculosis, especially if they are suffering from a severe form of diabetes. Von Noorden[60] found no cases of tuberculosis in 10 diabetics in the first decade of life, none out of

[51] Loc. cit.
[52] Virchow's Archiv, May, 1911, cciv, No. 2.
[53] Loc. cit.
[54] Der Diabetes Mellitus, 1893.
[55] Loc. cit.
[56] Loc. cit.
[57] Archiv. of Pediatrics, September, 1908.
[58] Diseases of Infancy and Childhood, 1905, p. 1136.
[59] Loc. cit.
[60] Loc. cit.

14 in the second, 2 cases of pulmonary tuberculosis out of 26 in the third, 3 out of 64 in the fourth, 4 out of 63 in the fifth, 5 out of 61 in the sixth, 1 of intestinal tuberculosis out of 49 in the seventh, and no cases of tuberculosis out of 2 diabetics in the eighth decade. The ages in the writer's 25 collected autopsies on diabetic patients are tabulated elsewhere.

THE FREQUENCY OF DIABETES AND GLYCOSURIA IN TUBERCULOSIS. Except for general statements to the effect that diabetes and glycosuria occur comparatively infrequently in tuberculosis, the literature has little to say on the subject. Richardson[61] writes, "On the whole, judging from experience, I should think that of 1500 cases of a phthisical character, not more than one would be a case of diabetic phthisis." Vibert[62] records 3 cases of glycosuria, usually slight, in 50 cases of tuberculosis. Abeles[63] found traces of sugar in 18 of 66 cases of far advanced tuberculosis.

The frequency of glycosuria and diabetes in the accompanying table is chiefly based on the reports from 25 tuberculosis sanatoria and hospitals in various parts of the United States. Out of 31,834 cases of tuberculosis there were 101 (about $\frac{1}{3}$ of 1 per cent.) cases of glycosuria and 51 (about $\frac{1}{6}$ of 1 per cent.) cases of diabetes. Some of the cases classed as glycosurics were undoubtedly diabetics, so that the percentage of diabetics may be assumed to be between $\frac{1}{3}$ and $\frac{1}{6}$ of 1 per cent. of all these tuberculous cases. From this table have been eliminated all sanatoria known to exclude diabetes or to fail to make urine examinations in all cases. The proportion of cases in the advanced stages of the disease is higher than the general average for all sanatorium cases in the United States. The autopsy figures show 5 cases of diabetes among 937 post mortems. It is possible that Adami and McCrae's cases of diabetes were admitted as diabetics and not as consumptives, as their report is based on general hospital cases and not on tuberculous cases which are all admitted primarily for their tuberculosis.

TUBERCULOSIS PRECEDING THE DIABETES. West[64] says that it is very rare for a patient with phthisis to develop diabetes mellitus. Raw[65] states that among 4000 cases of tuberculosis he cannot recall a single case with urine free from sugar on admission which developed diabetes mellitus. This has been the experience of the Phipps Institute and all sanatoria and physicians in communication with me on this point, except in regard to 2 or 3 cases reported to me as cases of primary tuberculosis, but unaccompanied by the data necessary to establish such a diagnosis. De Wolf[66] makes the general statement that the tuberculosis may be the primary disease. Shively[67] mentions a case which he considered developed

[61] Med. Times and Gazette, 1867, i, 219.
[62] Cited by Sauvage.
[63] Wien. med. Woch., 1874, p. 467.
[64] Loc. cit.
[65] Loc. cit.
[66] Jour. Amer. Med. Assoc., 1883.
[67] Loc. cit.

THE FREQUENCY OF DIABETES IN TUBERCULOSIS.

State.	Town or post office.	Institution or physician.	No. of cases of pulmonary tuberculosis reported on	No. of cases of glycosuria.	No. of cases of diabetes mellitus.
Colorado	Denver	Agnes Memorial Hospital	2200	2	2
Colorado	San Animas	United States Naval Hospital	1195	0	0
Connecticut	Hartford	Hartford Hospital	500	2	2
District of Columbia	Washington	Tuberculosis Hospital	1300	4	?
Illinois	Naperville	Edward Sanatorium	550	2	2
Maryland	Baltimore	Baltimore Municipal Tuberculosis Hospital	1315	2	2
Maryland	State Sanatorium	Maryland State Sanatorium	1200	4	4
Massachusetts	Rutland	Rutland State Sanatorium	1291	5	?
Missouri	Mt. Vernon	Missouri State Sanatorium	648	0	0
Missouri	St. Louis	Dr. Boisliniere	1321	1	1
New Jersey	Glen Gardner	New Jersey Sanatorium for Tuberculous Diseases	1472	4	?
New Mexico	Fort Bayard	United States Army General Hospital	3188	5	2
New Mexico	Fort Stanton	United States Marine Hospital Sanatorium	1884	11	4
New Mexico	Silver City	New Mexico Cottage Sanatorium	1050	5	5
New York	East View	West Chester County Tuberculosis Hospital	372	4	?
New York	Liberty	Workmen's Circle Sanatorium	245	0	0
New York	Loomis	Loomis Sanatorium	1338	7	3
New York	New York	Department of Health, Tuberculosis Sanatorium	2950	9	5
New York	Santa Clara	Hill Crest and Uplands	113	0	0
New York	Saranac Lake	Adirondack Cottage Sanatorium	340	0	0
North Carolina	Asheville	Winyah Sanatorium	1231	6	6
Ohio	Cincinnati	Cincinnati Hospital	1722	8	8
Pennsylvania	Philadelphia	Home for Consumptives	203	0	0
Pennsylvania	Philadelphia	Phipps Institute, University of Pennsylvania	3336	19	5
Pennsylvania	Pittsburg	Tuberculosis League	300	0	0
Wisconsin	Wales	Wisconsin State Tuberculosis Sanatorium	570	1	?
			31834	101	51

AUTOPSIES.

	Pulmonary tuberculosis.	Diabetes mellitus.
Reports of the Surgeon General, Public Health and Marine-Hospital Service, 1895 to 1905	373	0
Henry Phipps Institute until end of 1910	479	1
Adami and McCrae, Pulmonary Tuberculosis with Cavity Formation[a]	85	4
	937	5

[a] Loc. cit.

diabetes during pregnancy. I have entirely failed to meet with the record of a definite case of tuberculosis preceding diabetes, though one can hardly avoid assuming that this must take place at times. Healed and latent tuberculous lesions are being constantly encountered in cases of diabetes. In many cases it is impossible to tell whether the diabetes or the tuberculosis is the primary disease.

Duration of the Diabetes before the Onset of the Tuberculosis. This varies to some extent with the general conditions surrounding the patient just as does the mortality for tuberculosis. The age, the severity of the diabetes, and other factors also exert an influence on the development of tuberculosis in some cases. S. West asserts that tuberculosis does not, as a rule, appear in the acute cases of diabetes, and is rare in cases of less than two years' standing. Fox[69] says that tuberculosis commonly appears after the diabetes has lasted from one to two years. Purdy[70] considers that perhaps the majority of patients who have suffered from diabetes for more than two or three years are attacked by tuberculosis. Shively mentions 5 cases, in 1 of which the tuberculosis is said to have preceded the diabetes, while in the other 4 symptoms of tuberculosis developed eighteen, twelve, seven, and two months after the patients were known to be diabetic. In 3 cases collected by the writer in which the tuberculosis presented the appearances of a terminal infection the longest period preceding death after the detection of the first evidences of tuberculosis was three months and eleven days. Out of 17 cases from the records of the Hospital of the University of Pennsylvania, 6 gave a duration of the diabetes for periods of from five to seventeen years without any suspicion of tuberculosis.

Clinical Aspects of Tuberculosis in Diabetes. Diabetes may be complicated by all types of clinical tuberculosis, but a certain number of the cases are characterized by symptoms disproportionately slight in comparison to the extent and acuteness of the pulmonary disease. This modification of symptoms occurs particularly in those cases of advanced diabetes developing tuberculosis as an acute rapid terminal infection. The enfeebled state of these patients, somewhat as in old people developing tuberculosis, partly explains this change in the symptomatology, but more important, at least in some of the cases, is the rapid progress of the tuberculosis with fatal termination before the evolution of the pathological processes necessary to the production of some of the tubercular symptoms, such as hemoptysis and the presence of tubercle bacilli in the sputum, which are more liable to occur in cases of longer duration. Instead of being actually masked or diminished, however, the symptoms may be overlooked because attention is concentrated on the diabetic condition while the lungs are entirely neglected. In 3 cases of acute extensive tuberculosis investigated by the writer,

[69] Diseases of the Lungs and Pleura, 1891.

[70] Diabetes Mellitus, 1890.

no localizing pulmonary symptoms were recorded in one, cough and pain were the first symptoms in a second, coming on three and one-half months before death, and pain was the first symptom in a third preceding death by one and one-half months. The temperature has frequently been noted to be normal or below the average for tuberculosis, partly as a result of the lowered temperature peculiar to many diabetics. Shively found 4 out of 6 cases of tuberculosis complicating diabetes to be afebrile, while the temperature of the other 2 never exceeded 100°. On the other hand, a considerable rise of temperature in all of 4 cases of active tuberculosis, 3 being very acute and extensive, was encountered by the writer. The cough may likewise be slight and delayed until near the fatal termination. The expectoration may be slight and has been recorded as absent in some cases.

Hemoptysis. As in other symptoms of tuberculosis complicating diabetes, there is some difference in the experience of different observers as to the frequency of hemoptysis, though most clinicians have been impressed with its relative rarity. Von Noorden states that it occurs in about 12 per cent. of cases of tuberculosis complicating phthisis. Sanwith did not observe it in any of the cases coming under his notice in Egypt, and Williamson invariably failed to meet with it even in cases observed up until the time of death. Shively, on the other hand, found hemoptysis to be frequent and considerable in amount in 4 out of 6 cases. In 3 cases with extensive but acute tuberculosis of both lungs collected by the writer, there was no hemorrhage recorded, though the cases were observed in hospitals until the time of death.

Tubercle Bacilli in the Sputum. Tubercle bacilli appear in the sputum in large numbers according to Immerman and Rütimeyer, but the majority of writers consider that they occur rarely or not at all (von Noorden). Von Noorden himself failed to find them in 4 open cases with copious sputum, and in a fifth (far advanced) case only after repeated search were a few tubercle bacilli found. In the lungs from this patient the cheesy nodules and their walls revealed masses of tubercle bacilli. Shively in 6 cases found tubercle bacilli present in 3 and absent in 3. In a patient in the wards of the University Hospital who had acute extensive bilateral pulmonary tuberculosis with cavity formation, tubercle bacilli did not appear, in spite of frequent sputum examinations and the use of methods to concentrate the bacilli, until a week before death, and then only a few were detected.

Sugar in the Sputum. Bagou and a number of others report the presence of sugar in the sputum of tuberculous diabetics. Shively detected it in 1 out of 6 patients. Bussenius[71] detected sugar in the sputum in the proportion of 0.25 per cent.

[71] Cited by R. T. Williamson, Diabetes Mellitus, 1898.

PAIN. This subject is little if at all referred to in the literature, unless under individual case reports. In one case collected by the writer pain and cough were the first symptoms pointing to disease of the chest, both coming on three months and eleven days before death. Two days later friction rubs were audible. In another case of acute extensive tuberculosis, pain and cough developed about the same time, some six weeks before death.

TUBERCULIN. Sanwith[72] mentions 4 patients with diabetes complicated by tuberculosis, who received injections of Koch's tuberculin up to 10 milligrams. None of these reacted to the tuberculin, though 1 died suddenly of coma, and was proved at autopsy to have phthisis in the upper lobe of the right lung.

SWEATING. The effect of diabetes in lessening sweat secretion is asserted to occur even in the presence of tuberculosis. (Bagou.[73])

EFFECT OF TUBERCULOSIS ON DIABETIC SYMPTOMS. It is a common opinion that tuberculosis may lessen certain of the symptoms of diabetes. Williamson records 3 cases of diabetes complicated by tuberculosis with disappearance of glycosuria within a few days to six weeks before death. "With this disappearance of sugar the thirst and diuresis also ceased, and the whole clinical aspect of the cases, in the last stage of the disease, gradually changed from diabetes to phthisis with marked wasting." Purdy[74] considers the disappearance of sugar in the course of the lung complication a consequence of pyrexia. Sweet,[75] in experimental work on animals found no evidence indicating a decreased excretion of glucose during an infection. Futcher[76] considers it not unusual in diabetes with pulmonary tuberculosis accompanied by high fever, to see the sugar almost entirely disappear in the terminal stages. In one case investigated by the writer the sugar which at one time had reached 10 per cent. fell to 4.3 per cent. nineteen days before death. This patient had a very extensive and rapidly fatal form of tuberculosis of the lungs. and the acetone almost disappeared. Diabetic coma has been regarded as a rare occurrence in tuberculosis. One case has been recorded by Williamson, one has been reported to me by Dr. Riesman, and one occurred among the writer's collected cases.

PATHOLOGY OF TUBERCULOSIS COMPLICATING DIABETES. The Lungs and Pleura: Pulmonary tuberculosis in diabetes may appear in all the forms seen in tuberculosis uncomplicated by diabetes, but in diabetes it is supposed to be specially liable to take the form of a very rapid and extensive, usually caseous, tuberculosis, with early cavity formation, and with no tendency to cicatrization. This occurred in 3 of the writer's 6 cases. Tuberculous pleurisy appears in all its forms in diabetes, though

[72] Loc. cit.
[73] Paris Theses, 1888.
[74] Loc. cit.
[75] Jour. Med. Research, 1903-4, v. 255.
[76] Diabetes Mellitus, Osler's Modern Medicine, i, 774.

considered rare by Renon.[77] Pneumothorax has been described and pleural effusion though not encountered by the writer in the literature, occurred once among his collected cases.

The Larynx: The literature furnishes little but general statements about laryngeal tuberculosis in diabetes. A patient of this sort is at present attending the Phipps Institute Dispensary.

The Intestines: Tuberculous ulcers were found in the intestines twice in 92 autopsies on diabetic patients reported by Seegen,[78] the lungs being tuberculous in 40 of the cases. Among the writer's 6 collected cases there was no case of intestinal tuberculosis.

Meninges and Brain: I have been able to find only two references to tuberculous involvement of these structures in diabetes, one Rokitansky's case of meningeal tuberculosis cited by Seegen, the other De Jonge's[79] case of tuberculous involvement of the medulla oblongata.

The Liver: Seegen records 2 cases of tuberculosis of the liver in 92 post mortems on diabetic subjects and 1 case out of 30 in Rokitansky's series.

The Spleen: Miliary tuberculosis of the spleen has been reported by Pagou in a case of general miliary tuberculosis complicating diabetes. A questionable diagnosis of tubercles in the spleen was made in one of the writer's cases.

The Kidneys: Seegen reports tuberculosis of the kidneys twice in 92 post mortems on diabetic cases, Williamson once in 20.

The Adrenals: A case of adrenal tuberculosis in a diabetic subject occurred in one of the writer's series. (Described in the *Jour. of the Amer. Med. Assoc.*, March 23, 1912, lviii, 847.) Ogle[80] describes a case considered by Naunyn[81] to be one of tuberculosis of the adrenals.

The Peritoneum: One case of general tuberculosis of the peritoneum occurred among the writer's cases of diabetes. None was found in the literature.

The Lymph Nodes: I have found no record of tuberculous adenitis in diabetes except a general statement by Lloyd[82] and one case in the present series which showed tuberculosis of the bronchial and mesenteric glands.

Other Organs: The bones are infrequently found tuberculous in diabetes to judge from general statements. No reference could be found to tuberculosis of the heart, pericardium, genital organs, skin, or pancreas in diabetes.

Acute General Miliary Tuberculosis. Bagou[83] has reported a case of diabetes with good clinical and pathological notes in which

[77] Arch. Gén. de Méd., Paris, 1903, i, 528.
[78] Der Diabetes Mellitus, 1893.
[79] Cited by F. T. Frerichs, Ueber den Diabetes, 1884, p. 136.
[80] St. George's Hospital Reports, 1866, i, 178.
[81] Der Diabetes Mellitus, 1906, p. 55.
[82] Post-Graduate, 1906, xxi, 637.
[83] Paris Theses, 1888.

the lungs, liver, and spleen were filled with miliary tubercles. It is considered by many to be a rare disease in diabetes.

Bacteriology of the Lungs in Tuberculosis Complicating Diabetes. Besides tubercle bacilli, which may be found in profusion in the lungs even when few or absent in the sputum, various other microörganisms may be associated with the tubercle bacillus. Honl[84] considers that tuberculosis complicating diabetes is usually a polymicrobic infection. Ehret[85] attaches much importance to the influence of secondary or mixed infections in the tuberculosis of diabetes. He believes that there is a more varied and more luxuriant growth of organisms than in uncomplicated tuberculosis.

Prognosis of Tuberculosis and Diabetes. To judge from the literature and from reports received from a number of sanatoria, the experience of many physicians has been that the association of tuberculosis and diabetes in the same patient offers a gloomy outlook, and some assert that it is practically always fatal. While admitting the greater seriousness of two diseases, one is struck with the number of cases in which the tuberculosis and the diabetes seem to pursue quite independent courses in the same individual, each responding to treatment or neglect, and each requiring a prognosis based entirely on its own merits. Von Noorden mentions a patient with pulmonary and laryngeal tuberculosis and 4 per cent. of sugar, whose sugar, with appropriate treatment, fell to 0.5 per cent., whose larynx became healed, whose expectoration ceased, and who was in good health nine years later. At present there is in attendance at the Phipps Institute a patient who was admitted a year ago with pulmonary and laryngeal tuberculosis and diabetes (sugar, 5.5 per cent., specific gravity, 1040) whose condition is at present quite satisfactory, the lung condition being almost arrested, though the amount of sugar has not greatly varied. Reports from a number of physicians based on experience in private practice and sanatoria has yielded 11 definite cases ending fatally, 1, however, in coma and not as a result of his tuberculosis. Of 3 not ending fatally, 1 improved temporarily and later was lost sight of, 1 improved in his pulmonary and general condition although the amount of sugar remained stationary, and the third case, in spite of a large amount of sugar, showed improvement in his tuberculosis and lost his sugar.

Important factors determining the prognosis of tuberculosis complicating diabetes are: (1) The condition of the patient, each disease having to be considered separately, and the combination also having to be estimated so far as possible; and (2) the use or neglect of appropriate treatment for each disease. Of particularly bad omen is the acute rapidly extending form of tuberculosis

[84] Wien. klin. Rundschau, 1898, xii, 245, 265, 299.
[85] Münch med. Woch., 1897, xliv, No. 52.

coming on late in the course of diabetes, and behaving in the manner of a terminal infection. In many cases, however, the prognosis as to the tuberculous condition may be made at least tentatively along the same lines as in uncomplicated tuberculosis. The glycosuria is not aggravated by the tuberculosis. One should always think of the possible occurrence of tuberculosis as a terminal infection in diabetes. A number of French writers have stated that diabetes dependent on lesions of the pancreas usually ends fatally in tuberculosis in a comparatively short period, while the gouty (arthritic, constitutional, hereditary) type, as they call it, commonly showing 3 to 4 per cent. of sugar and often lasting twenty-five to thirty years, may resist tuberculous invasion for a long time. Sauvage considers that an excess of uric acid in the blood antagonizes the development of the tubercle bacillus. He adds that tuberculous patients improve on hyperalimentation with nitrogenous foods, and states that carnivorous animals are rarely affected and herbivorous animals are often affected with tuberculosis. This subject has recently been referred to by Raw, who says that the treatment of tuberculosis should aim at the production of an artificial gout.

Treatment of Diabetes Complicated by Tuberculosis. This important subject can only be very briefly alluded to here. While there are times when either the diabetes or the tuberculosis demands special treatment which ordinarily would be contraindicated for the other disease, the cases are fortunately comparatively few in which proper treatment for one of the diseases seriously interferes with successful results in the other. General tuberculosis treatment tends to help the diabetic by rendering him less liable to this form of infection. A diet providing a considerable proportion of milk and eggs is often well borne in both conditions. Every precaution should be taken by the diabetic patient to avoid the development of tuberculosis both from germs that may be harbored by himself, and from those he may be exposed to through his surroundings.

Summary of Cases. Out of 111 cases of diabetes collected in the hospitals of Philadelphia, 9 had active pulmonary tuberculosis, and 1 other had adrenal tuberculosis. Out of 51 non-fatal cases of diabetes, none had active pulmonary tuberculosis. Out of 60 fatal cases of diabetes, 9 had active pulmonary tuberculosis and 1 other had adrenal tuberculosis. Out of 35 fatal but non-autopsied cases of diabetes, 3 had active pulmonary tuberculosis. Out of 25 post mortems, 6 showed active pulmonary tuberculosis and 1 tuberculosis of the adrenal gland without tuberculosis elsewhere. Out of 86 non-autopsied cases (35 fatal) 3 had active pulmonary tuberculosis and 17 more had signs recorded that were only slightly suggestive of tuberculosis.

Physical signs in 86 non-autopsied cases (35 being fatal):

Normal, 56; signs of active pulmonary tuberculosis (all fatal cases), 3; signs slightly suggestive of tuberculosis, but without diagnosis of tuberculosis, 17; abnormal signs not suggesting tuberculosis, 10.

Condition of the Lungs in 25 Autopsies on Diabetic Cases: Ten cases with pulmonary tuberculosis. Very acute and extensive tuberculosis, 3; mixed chronic and acute, not very extensive tuberculosis, 1; chiefly chronic, slight acute tuberculosis, not very extensive, 1; acute, not extensive, 1. Active, 6 cases. Latent tuberculosis, 1; calcareous (tuberculous?) foci, 1; caseous tuberculous nodule in lung, 1; caseous tuberculous nodule in lung, pleural adhesions, 1. Non-active, 4 cases.

Fifteen cases with no pulmonary tuberculosis. Normal, 2; chronic fibroid pleurisy, 3; congestion, edema, or emphysema, 4; croupous pneumonia, 3; septic infarct, 1; multiple infective infarcts, septic pneumonia, abscesses, 1; abscess and gangrene (adrenal tuberculosis without tuberculosis elsewhere), 1.

Ages of 25 Cases Autopsied in Relation to Tuberculosis: Twenty to thirty years, 5; active pulmonary tuberculosis, 2. Thirty to forty years, 5; active pulmonary tuberculosis, 2. Forty to fifty years, 2; active pulmonary tuberculosis, 0; adrenal tuberculosis, 1. Fifty to sixty years, 7; active pulmonary tuberculosis, 2. Sixty to seventy years, 2; active pulmonary tuberculosis, 0. Seventy to eighty years, 2; active pulmonary tuberculosis, 0. No record, 2; active pulmonary tuberculosis, 0.

Lungs in 4 Autopsies on Colored Persons: Active tuberculosis, 1; Chronic adhesive pleurisy, 1; croupous pneumonia, 1; normal, 1.

Clinical and Pathological Diagnosis in 7 Cases of Diabetes, 6 Complicated by Active Pulmonary Tuberculosis and 1 by Adrenal Tuberculosis. Case I.—Male, aged fifty-one years; white. Pulmonary tuberculosis very acute and extensive. Clinical diagnosis: Diabetes mellitus; chronic diffuse nephritis. Pathological diagnosis: Double pleural effusion; chronic adhesive pleurisy; miliary tuberculosis of the lungs and tuberculous bronchopneumonia; miliary tuberculosis of the spleen (?); adhesions of the sigmoid flexure; cardiac (left ventricular) dilatation; fibroid myocarditis; atheroma of the coronary arteries and aorta; chronic mitral and aortic sclerotic valvulitis; chronic interstitial nephritis; renal arteriosclerosis; perilobular hepatic cirrhosis; splenic arteriosclerosis; chronic gastritis; pancreas normal but small.

Case II.—Male, aged twenty-seven years. Pulmonary tuberculosis very acute and extensive. Clinical diagnosis: Banti's disease; diabetes mellitus; phthisis pulmonalis. Anatomical diagnosis: General tuberculous peritonitis; tuberculous pleuritis, and pleural adhesions; tuberculosis of the lungs (caseous and gelatinous pneumonia with cavity formation); splenomegalia

(Banti's disease); slight chronic interstitial hepatitis (?); slight chronic mitral endocarditis; fatty degeneration of heart and kidneys.

CASE III.—Male, aged twenty-one years; white. Pulmonary tuberculosis very acute and extensive. Clinical diagnosis: Pulmonary tuberculosis; diabetes mellitus. Anatomical diagnosis: Pulmonary tuberculosis; mucoid degeneration of epicardium; slight chronic aortic valvulitis; congested and slightly cirrhotic liver; chronic perisplenitis; congestion of kidneys; moderate cirrhosis of pancreas; mucoid change of peritoneal fat. Histological diagnosis: "Endothelial catarrh" of tuberculous lymph glands (bronchial and mesenteric) with external pigmentation and congestion; miliary tuberculosis of lungs, cavities, and congestion; pleural adhesions and obliterative pleurisy; slight interstitial hepatitis; renal congestion, cloudy swelling, and fibrosis (moderate); slight chronic interstitial pancreatitis; moderate splenic congestion; arteriosclerosis (slight) and hyaline change (slight) in diaphragm.

CASE IV.—Male, aged fifty-eight years, white. Pulmonary tuberculosis, chronic and acute, not extensive. Clinical diagnosis: Tuberculosis of the lungs; diabetes mellitus; arteriosclerosis. Anatomical diagnosis: Caseous ulcerative tuberculosis of the lungs; congestion and edema of lungs; pleural adhesions; slight fibrosis of the kidneys. Histological diagnosis: Caseous tuberculosis, edema, and congestion of the lungs with anthracosis; fibrosis and congestion of the spleen; red atrophy of liver, fatty infiltration, hemosiderin, biliary cirrhosis; chronic interstitial nephritis.

CASE V.—Male, aged thirty-two years; white. Pulmonary tuberculosis chiefly chronic, slightly acute, not very extensive. Clinical diagnosis: Diabetes mellitus. Pathological diagnosis: Obliterative pleurisy of the right side; chronic pulmonary tuberculosis with cavity; chronic valvular endocarditis; chronic interstitial nephritis; atrophy of pancreas.

CASE VI.—Male, aged thirty-three years; colored. Records very incomplete. Pulmonary tuberculosis, acute, but not very extensive. Clinical diagnosis: Diabetes mellitus. Autopsy—Lungs: Both apices showed a large tubercular patch caseating and full of greenish pus, otherwise normal. Heart: Negative. Liver: Normal, infiltrated slightly with fat. The kidneys were decidedly infiltrated with fat and congested.

CASE VII.—Male, aged forty-five years; white. Adrenal tuberculosis (none elsewhere). Clinical diagnosis: Diabetes mellitus; pulmonary tuberculosis. Anatomical diagnosis: Atrophy of the right adrenal; gangrene and abscess of lungs; acute serofibrinous pleuritis; fatty degeneration of heart and kidneys; chronic interstitial pancreatitis; arteriosclerosis; acute splenic tumor; multiple superficial erosions of esophagus. Atrophy of the thyroid gland (?). Histological diagnosis: Tuberculosis of adrenals,

slight chronic interstitial pancreatitis. Bacteriological diagnosis: Streptococcus pyogenes; Staphylococcus pyogenes aureus; Bacillus coli communis.

SUMMARY. That tuberculosis occurs more frequently in diabetes than in the general population at the same age periods has not been definitely proved by the evidence collected by the writer. However, one is impressed by two facts: (1) The lowered opsonic index to the tubercle bacillus and a number of other bacteria in diabetes; and (2) the large number of cases of diabetes late in the course of the disease developing a very acute, extensive, and rapidly fatal form of pulmonary tuberculosis. Tuberculosis occurs more frequently in diabetes than in some other chronic diseases. The frequency of tuberculosis in diabetes varies with a great variety of different circumstances. In the writer's 25 collected autopsies on diabetic patients, 6 showed active pulmonary tuberculosis varying in acuteness and extent of involvement, and 1 showed adrenal tuberculosis without tuberculosis elsewhere. Out of 355 autopsies collected from the literature since 1882, including also the writer's 25 cases, 138 (38.9 per cent.) revealed pulmonary tuberculosis, mostly in an acute form. In some structures, for example, the bones, the writer could not find a single case of tuberculosis in a diabetic patient.

The frequency of diabetes in cases of tuberculosis is fairly well represented by the table presenting 31,834 cases of pulmonary tuberculosis, of which about $\frac{1}{3}$ of 1 per cent. had glycosuria, and between $\frac{1}{6}$ and $\frac{1}{3}$ of 1 per cent. had diabetes. Five cases of diabetes were found in 937 autopsies on tuberculous patients.

When diabetes and tuberculosis are associated the diabetes can usually be shown to be the primary disease, in a number of cases it is impossible to show which is the primary disease, and in no case that the writer has encountered has the tuberculosis been definitely proved by the evidence furnished to be the primary disease.

When diabetes and tuberculosis are associated in the same patient either disease may show certain modifications in course and symptomatology, but often each disease runs a course apparently independent of the other.

Like the clinical course the autopsy findings may reveal nothing unusual in regard to the tuberculosis, but in a number of cases one meets a tuberculous process that is marked by acuteness, extensiveness of the disease, and tendency to the early development of cavity formation.

From the number of cases that have improved both as to their tuberculosis and their diabetes, one cannot consider the combination of diabetes and tuberculosis as necessarily more hopeless than the diabetes or the tuberculosis alone. The prognosis in many cases depends largely on the treatment.

Space does not allow me to give due thanks and credit to those who are largely responsible for what may be of value in this paper. To Dr. H. R. M. Landis, Dr. Paul Lewis, Dr. E. J. G. Beardsley, Dr. A. J. Smith, Dr. W. M. L. Coplin, Dr. David Riesman, Dr. I. Kaufman, Dr. C. Y. White, Dr. R. S. McCoombs, Dr. W. B. Bartlett, Dr. R. D. Lyman, and Dr. P. C. Bartlett, I am particularly grateful for information or suggestions. To the physicians of the University, the Pennsylvania, the Episcopal, the Jefferson, the Children's, and the Philadelphia Hospitals I am indebted for the use of records, and to the physicians of a number of sanatoria throughout the United States for important information, and especially to Dr. F. C. Smith and his assistants, of the United States Public Health and Marine-Hospital Service, Fort Stanton, New Mexico, who have furnished me with invaluable data at considerable expenditure of time and labor.

A FURTHER STUDY OF THE PROGNOSTIC VALUE OF ARNETH'S LEUKOCYTIC BLOOD PICTURE IN PULMONARY TUBERCULOSIS, BASED UPON 729 COUNTS IN 475 PATIENTS.[1]

By Paul H. Ringer, A.B., M.D.,

Asheville, N. C.

Three years ago, in a paper by Dr. C. L. Minor and myself,[2] there were reported the results of the first 100 Arneth counts done by us together with deductions as to their probable prognostic value in cases of pulmonary tuberculosis. At this time it is unnecessary to go into the theory of the causation of this blood picture and its variations. Suffice it to say that the blood picture consists in a differential count of the polymorphonuclear neutrophiles with respect to the number of their nuclei. Five classes are recognized according to the number of nuclei in this variety of leukocyte. Arneth claims that in cases with low resisting power there is a preponderance of cells with one or two nuclei, while in cases with good resisting power the percentage of leukocytes with three, four, and five nuclei is increased. Thus in bad cases he obtains what he terms a shifting of the blood picture to the left—"Verschiebung nach Links." This blood picture has been studied and Arneth's conclusions substantiated by many workers, including Arloing and Genty, Bushnell and Treuholtz, Edson, Klebs, Webb

[1] Read before the National Association for the Study and Prevention of Tuberculosis, Washington, D. C., May 31, 1912.

[2] Amer. Jour. Med. Sci., May, 1911.

and Williams. The work of Dr. Minor and myself agreed in the main with the results obtained by those mentioned above. We elected to divide our cases according to the clinical symptoms rather than according to the amount of lung involvement, and grouped them into four classes: (1) Good, (2) medium, (3) bad, (4) very bad. Upon going over our counts and making a graphic representation of the results, we found that the one and two nuclei cells were greatest in the classes named "bad" and "very bad," and decreased in the classes named "good" and "medium," while the opposite was true of the cells with three, four, and five nuclei. In a small number of cases—not over 4 or 5—we found together with a good clinical symptom complex a very bad blood picture, and we noted that shortly thereafter the patient took a turn for the worse.

Neither in the counts forming the basis for the paper above referred to, nor in the counts following it, have the polymorphonuclear leukocytes been divided into sub-classes (as Arneth was wont to do) based upon the shape of the nuclei—whether indented, S-shaped, crescentic, etc. This has been deemed unimportant. The same arbitrary rules for counting that were advocated in the article written three years ago have been strictly adhered to. These are: (1) Nuclei connected by an isthmus counted as one nucleus. (By "isthmus" is meant a strand of nuclear matter one-third or more of the thickness of the nucleus.) (2) Nuclei connected by a thread counted as two nuclei. (3) Nuclei clearly superimposed counted as two nuclei. (4) Nuclei tangent to one another counted as two nuclei. Thus uniformity of counts done by the same worker was assured.

So much for a very brief review of the former results published by Dr. Minor and myself. Since that time the use of Arneth counts has been continued, and the writer wishes in this article to set forth conclusions arrived at from a total of 729 counts done on 475 patients. In addition to the counts done on tuberculous or supposedly tuberculous patients, the blood of 20 apparently normal individuals has been counted, in order to arrive at a "normal" blood picture.

The average of these 20 counts gives as a normal blood picture the following:

	I	II	III	IV	V	Index
Percentage	4	20.5	58.5	15	2	53.75

This average is slightly better than that obtained by Arneth from the average of 15 supposedly normal individuals. His "normal" blood picture reads as follows:

	I	II	III	IV	V	Index
Percentage	5	35	41	17	2	60.5

The "index," so-called, is one arbitrarily adopted by Bushnell, and is obtained by adding together the percentages of Classes I and II, and half that of Class III, thus showing what percentage of the cells is to the left in the blood picture. This index has the advantage of showing at a glance whether the blood picture is good or bad, but it has the disadvantage that it tends to relegate into the background the relative proportions of the various classes, and especially that it recognizes no difference between Classes I and II, a difference that is not without importance.

As a result of over 700 counts, the conclusions drawn can be neither as unified nor as satisfactory as those derived three years ago from 100 counts; showing that greater familiarity with a method both enhances its value and indicates its limitations. The writer does not wish to be thought to mean that the Arneth blood picture is to be considered as valueless, misleading, or false. Far from it. The blood picture is of a certain value, it should not be abandoned, and it will in certain apparently favorable cases correctly presage an unfortunate outcome, or *vice versa*. The writer, however, must confess that he cannot place as much weight upon its prognostic value as he did three years back.

First and foremost it must be distinctly understood that the Arneth blood picture can in no way be taken to indicate the amount of lung involvement or the stage of the disease. It is simply and solely an index of the resisting power of the patient. Patients with extensive local lesions—usually of the fibroid type—showing but little activity and having a good general state of nutrition will give a relatively good blood picture; while others with but very slight local lesions, but poor nutritional conditions will give a bad picture. As an example of the first class may be cited the blood picture of a man (J. B. McG.) with fibroid phthisis of fifteen years duration—extensive pulmonary involvement, but good general condition:

	I	II	III	IV	V	Index
Percentage	12	45	35	7	1	74.5

This is a relatively good blood picture, especially when contrasted with that of the following patient (McD.) having but suspicious signs of a unilateral basal pleurisy, no cough, no bacilli in the very scanty sputum, but in very poor general condition. His blood picture was as follows:

	I	II	III	IV	V	Index
Percentage	12	42	42	4	0	75

Which is decidedly bad for a patient with such slight evidences of disease.[3]

[3] Since the writing of this paper the patient here referred to reacted violently to 2 mg. of old tuberculin.

Again, improvement in the blood picture or the reverse, indicates a corresponding change in the resisting powers of the patient and that alone. To be sure such changes are usually accompanied by betterment or further extension of physical signs, but there are always patients to be found whose general condition improves markedly while the physical signs remain stationary, just as there are others that begin to go downhill without any detectable change taking place in the local pulmonary condition. It is in such cases that the blood picture is of distinct value. The 3 following cases will illustrate this point:

CASE I.—In a patient running no fever (W. B.), and with slight unilateral apical catarrh, the following relatively bad picture was found:

	I	II	III	IV	V	Index
Percentage	20	45	36	5	0	80

One month later the reading was:

	I	II	III	IV	V	Index
Percentage	38.5	49.5	10.5	1.5	0	93.5

This was soon followed by an acute exacerbation of his disease which shortly ended fatally.

CASE II.—The patient (Col. B.), a man in excellent condition, showed but the faintest signs of pulmonary involvement—granular or rude breathing at the right apex anteriorly and posteriorly. His blood picture on arrival was:

	I	II	III	IV	V	Index
Percentage	3	29	55	12	1	59.5

Seven weeks later, fourteen pounds having been gained, but the physical signs being identically the same, he showed:

	I	II	III	IV	V	Index
Percentage	4	20	56	18	2	52

CASE III.—A man (Rev. M. L. B.) of slender build and excessively nervous temperament, pale, anemic, and generally run down, showed at both apices definite breath changes, but no adventitious sounds. His blood picture on arrival was:

	I	II	III	IV	V	Index
Percentage	36	48	16	0	0	92

This pointed to an unfavorable termination, despite the slight physical signs. Three months later, having gained much in weight and strength, his lungs showed in addition to the modified breath sounds a few fine crackles at one apex anteriorly and posteriorly. The blood picture at this time, however, showed the following:

	I	II	III	IV	V	Index
Percentage	24	42	27	7	0	79.5

A great improvement substantiated by the man's general condition, despite the increase in physical findings.

These 3 cases serve to stress the point that by means of the Arneth blood picture we obtain an index of the general resisting power of the patient, and of that alone.

In mentioning the index used in the blood picture it was stated that it was apt to be misleading by taking the attention away from the percentage of cells in the various classes, and making no differentiation between Classes I and II. The following case well illustrates this point: A patient (F. R. H.) with marked pulmonary and slight laryngeal involvement showed upon arrival the following bad blood picture:

	I	II	III	IV	V	Index
Percentage	31	46	20	1	2	87

Two and a half months later, having made great improvement, his picture was as follows:

	I	II	III	IV	V	Index
Percentage	15	53	27	5	0	81.5

No very striking difference is seen upon looking at the indices, but it must be noted that the cells in Class I are reduced by over 50 per cent., and the cells in Class IV increased 500 per cent., this being significant despite the loss of cells in Class V.

In the writer's opinion a bad blood picture with the percentage in Class I in excess of that in Class II is far worse than one in which the members of Class II are in the majority.

So far attention has been called to counts tending to prove the value of the blood picture in estimating the resisting power of the patient, and consequently in shaping our prognosis. In all fairness the other side of the question must now be taken up, and cases cited in which the blood picture has been misleading.

It is an undeniable fact that in a small number of cases the blood picture has been at absolute variance with the clinical picture, and the subsequent course of the case has in no way accounted or atoned for the anomalous blood findings. It has been quite impossible to estimate exactly the percentage of cases in which this condition has been found, because of the impractibility of eliminating external (and also internal) agencies that could not be foreseen and that had either a salutary or else a deleterious effect upon the patient. In the writer's opinion about 5 per cent. of the cases show a blood picture totally at variance with the clinical picture, and not borne out by subsequent events. This occurs chiefly in cases with good general symptoms and satisfactory local signs. Two examples will suffice:

CASE I.—A patient (R. S.) came to Asheville in March, 1909, with but slight physical signs and in excellent general condition. However, from the character of the onset of the disease and from the quality of the signs, the trouble was suspected to be of an acute nature. Upon arrival the blood picture was as follows:

	I	II	III	IV	V	Index
Percentage	21	55.5	21	2.5	0	87

Two months later, the patient having markedly improved, the picture read:

	I	II	III	IV	V	Index
Percentage	23	47.5	29	0.5	0	85

There was practically no change.

Two months later, the general and local condition having shown still further improvement, the picture remained unchanged, to wit:

	I	II	III	IV	V	Index
Percentage	20	48	32	0	0	84

The patient has been heard from recently, and is now well and in the best possible condition.

CASE II.—Another patient (R. S. R.) came under observation with but very slight unilateral apical catarrh—no temperature—general condition excellent. The blood picture was distinctly at variance with what would be expected. It read:

	I	II	III	IV	V	Index
Percentage	19	52	23	6	0	82.5

The patient has improved, and is in most satisfactory condition, but the last count done reads as follows:

	I	II	III	IV	V	Index
Percentage	17	55	24	3	1	84

This count shows practically no change.

It would be wearisome to give more examples. The 2 cases cited amply illustrate the point.

Solis Cohen and Strickler[4] have made a careful study of the Arneth blood picture in cases of pulmonary tuberculosis. Their conclusions are here set forth.

"While the average index showed little change, in most of our individual cases the proportion of cells in the first two classes of Arneth seemed to be increased as the patient improved, and in a number of cases to be decreased as the patient grew worse. Of 27 improving patients whose blood was examined more than

[4] AMER. JOUR. MED. SCI., November, 1911.

once, an increase in cells with one and two nuclei was observed in 22, and a decrease in 4. Among advancing cases there was an increase in 3, a decrease in 4, and no change in 2. Our figures are opposed to those of all other workers."

Such statements from such reliable authorities deserve serious consideration. It is quite impossible for the writer to explain the discrepancy. It would hardly be likely that the majority of Cohen and Strickler's cases were of the type exemplified by the last two examples cited. The only other way for accounting for the contradictory findings is difference in the method of counting the nuclei, for in certainly 50 per cent. of the cells the nuclei are so placed or so connected that a doubt will arise as to which class the particular cell belongs. Were it possible for all workers in this field to agree upon a common set of rules for the estimation of the number of nuclei, and, furthermore, were it possible for different workers to count each other's smears, the real value of the method would be far better shown.

In a masterful paper on this subject which unfortunately came to the writer's notice but recently, Miller and Reed[5] point out that the nuclei are greatly affected as to their number by the fact of either finger or slide being contaminated with dirt. This is a distinctly valuable point, and also a prolific source of error. It is gratifying to note that such painstaking workers as those just cited, believe that the Arneth blood picture is of real value in prognosis.

In conclusion, the writer would state that in his opinion the Arneth blood picture has a certain definite value in forming a prognosis in pulmonary tuberculosis. It is a corroboratory factor to the general clinical picture, and should never be given much weight in contradiction to the general symptom complex presented by the patient. In a small number of cases it will presage an unfortunate outcome or else will cause us to pause before giving a bad prognosis. In a small number of cases it will remain opposed to all the general indications found in the patient. In the vast majority of cases it will faithfully represent the patient's resisting powers but will not disclose any new features. The Arneth blood picture is to be viewed with conservatism. Few that take it up and study it carefully will ever abandon it entirely, but he that places implicit confidence in its readings and bases his prognostic opinion chiefly thereon, will not infrequently be led into error.

[5] Archives of Internal Medicine, May 15, 1912.

CHANGES IN THE KIDNEY RESULTING FROM TYING THE URETER.

By J. F. Corbett, M.D.,

ASSOCIATE PROFESSOR OF EXPERIMENTAL SURGERY, UNIVERSITY OF MINNESOTA.

Clinicians agree that atresia of the ureter usually results in hydronephrosis of the corresponding kidney, and that this may remain as a final result or be followed by secondary atrophy. The picture is much the same, whether the condition arises from congenital stenosis of the ureter, or from some sudden blocking of that structure by any cause. The effect on the patient, over and beyond that resulting from the loss of functionating kidney parenchyma, is not definitely and clearly established.

Many of the patients having congenital or long-standing stenosis of the ureter have lived to a ripe old age without having experienced any untoward symptoms. On the other hand, fully as many patients have been driven to seek surgical relief on account of a similar pathological condition.[1]

For a thorough review of this part of the subject, the reader is referred to articles by Allen and Parker,[2] C. N. Dowd,[3] Bottomley,[4] and Eisendrath.[5]

In the series of cases reviewed by Bottomley,[6] there were 3 instances where changes corresponding to some form of nephritis occurred in the non-occluded kidney. In 2 of these cases, 1 reported by Sainsbury,[7] and 1 by Cooper Rose,[8] the probable added factor of a low grade infection must be considered. But in Bostrem's[9] case, where marked changes occurred in the non-occluded kidney, the hydronephrotic fluid did not give any evidence of infection. Further than this, Ord[10] reports a death resulting from a stricture of the ureter, and White[11] a case of coma from a similar condition. From the records of these observers, one is scarcely justified in drawing definite conclusions, except that the results of an atresia of one ureter vary greatly in different individuals.

Turning from the clinical consideration to the experimental laboratory, we find that this subject has received considerable attention. As the conclusions of laboratory workers have not always been identical, I feel justified in reviewing the most important work of the observers.

[1] Louis Frank, New York Med. Jour. 1912, p. 410.
[2] Annals of Surgery, xlii, 265.
[3] Surg., Gyn., and Obstet., xii, 533.
[4] Jour. Exp. Med., ix, 82.
[5] Ibid., lii, 597.
[6] Loc. cit.
[7] Trans. Path. Soc., London, xxxvii, 296.
[8] Cited by Bottomley, Annals of Surgery, lii, 624.
[9] Ibid., p. 616.
[10] Trans. Path. Soc., London, xlvi, 132.
[11] Trans. Path. Soc., London, xxxviii, 168.

Nefedieff[12] found marked changes in remote organs and in the opposite kidney as a result from the ligation of one ureter. Nefedieff assumes that these remote changes were due to a nephrotoxic substance in the blood. No other observer has ever been able to confirm the existence of any such substance, but the important part of Nefedieff's work is that he found changes in the unoperated kidney. That changes such as occur in the non-operated kidney could be due to absorption of nephrotoxic substances from the cells of the normal kidney, is negatived by the work of Miss B. Sheldon Amos.[13] Pearce[14] and Aronson[15] also show that the extracts of normal kidneys have no more specific action than cholin derived from any source.

The rabbits in which Miss Amos ligated one ureter, frequently died, and the protocols from these experiments show that there were more or less important changes, such as cast formation or new connective tissue in the unoperated kidneys in about 50 per cent. of the animals. Miss Amos suggests that death occurring at very irregular intervals in these animals was due to some toxic substance elaborated by the operated kidney, and stored in its hydronephrotic sac. Death certainly could not have been due to the loss of function of one kidney, for Sampson[16] and Pearce[17] have established that only one-third of the total kidney substance is necessary to life.

Pearce[18] found the essential lesion of atresia of one ureter to consist of changes in the operated kidney, and only compensatory hypertrophy in the other kidney.

Lindeman,[19] Castaigne and Rathery,[20] Nefedieff,[21] and Sollman, Williams, and Briggs[22] have pictured changes in the tied side. Pearce[23] and Amos[24] confirm these findings.

The length of time necessary to bring about complete destruction of the kidney, as far as its functioning capacities are concerned, has been considered by Sollman, Williams, and Briggs.[25] Inasmuch as the contained hydronephrotic fluid was found not to be urine, but transudate, after four weeks atresia of the ureter, this may be assumed as the minimum time.

This paper will discuss the following conditions: (1) Changes resulting from ligature of the ureter in the kidney on the tied side. (2) The amount of function remaining to the kidney after atresia of the ureter lasting for various periods of time. (3) Lesions remain-

[12] Annales de l'Institut Pasteur, 1901, xv, 17.
[13] Jour. Path. and Bact., x, 265.
[14] Jour. Exp. Med., xi, 430.
[15] Jour. Med. Research, xxi, 313.
[16] Jour. Exp. Med., x, 745.
[17] Ibid., x, 632.
[18] University of Pennsylvania Med. Bull., 1903, p. 217 (cited by Miss Amos).
[19] Zentralbl. f. allgemein Path. und path. Anat., vi, 184.
[20] Compt. rend. Soc. Biol., 1902, p. 653 (cited by Miss Amos).
[21] Loc. cit.
[22] Jour. Exp. Med., ix, 71.
[23] Loc. cit.
[24] Loc. cit.
[25] Loc. cit.

ing in the kidney as a permanent legacy after tying the ureter, and at a subsequent date removing the ligature. (4) Changes in the unoperated kidney.

The ureters were all ligated in the following manner:

Under full ether anesthesia, the abdomen was opened, and after the intestines were packed off, the ureter with a bit of the underlying fascia, was surrounded by a single linen thread. This was tied tight enough to produce atresia without cutting the tissues.

After the operation, the animals were kept in special metabolism cages, and fed a diet of known chemical composition. A record was kept of the animals' condition, and all the urine and feces saved for analysis. In all, twenty-four animals were sacrificed.

FIG. 1.—Animal experiment 11-56. Left ureter ligated for twenty-four hours. On the left is shown the operated kidney; on the right the control.

1. RESULTS OF ATRESIA OF URETER ON THE OPERATED KIDNEY. The most striking changes produced by atresia of the ureter are those closely resembling the lesions of nephritis, as the following examples typify. The kidney with a twenty-four-hour stenosis of the ureter, is larger and heavier than on the control side, and presents alternating light and dark areas. The glomeruli are sometimes encircled by a zone of congestion. The convoluted tubules in places are nearly normal, in other places appear to have undergone an extreme degree of degeneration, so that in place of normal epithelial cells lining these structures, we have left only a mass of granular detritus. The tubules of the kidney generally are dilated, and this dilatation is more marked as we approach the pelvic outlets of the collecting tubules. The kidney of which the ureter had been ligated for six days, presents a still more striking appearance as it is very pale and edematous, with increase of size and weight. The pelvis shows marked hydronephrosis. There is general deformity of the tubules, extensive degenerative changes

in the convoluted tubules and the beginning formation of new connective tissue. In the collecting tubules masses of detached epithelium are frequently seen. At the end of twenty-six days, a ligated kidney presents an extreme picture of hydronephrosis, so that it is actually converted into a very thick-walled cyst. The kidney substance is white and is cut with difficulty. On the surface are retracted areas corresponding to bands of connective tissue seen on the cut surface. Under the microscope the cortex consists of a mass of connective-tissue cells, round cells, dilated and deformed tubules, nearly normal glomeruli, and all stages of cast formation.

FIG. 2.—Animal experiment 11-61. Left ureter ligated for twenty-six days. On the left is shown the operated kidney: on the right the control.

These pictures are the most striking examples encountered in a series of four animals for each period of time. In some of the animal experiments, the changes given above appear to so slight a degree as to seem almost negligible. In these cases deformity of the tubules and fatty metamorphoses are marked. In the twenty-four-day series, the extent of destruction of the parenchyma seems to be about the same whether the picture is that of fatty change or that of nephritis. In a very few instances the damage is erratic in that it is localized.

2. The histological findings in this series indicate very extensive destruction of the kidney substance on the operated side, as the result of tying one ureter. To determine whether enough of the kidney parenchyma was destroyed by these processes to ablate the secretory function of the kidney, the urine was collected from kidneys whose ureters had been so occluded for various periods of time, measured, and analyzed.[26] In Table I, under Animal Experiment, 11–58, the nitrogen content shows that the kidney

[26] Annals of Surgery, xliii, 725.

the ureter of which had been ligated for twenty-four hours was for a time capable only of excreting urine in a very irregular manner. This kidney in time resumed its full function. The amount of chloride excreted also varied from day to day, but showed less general departure from the normal than the nitrogen.

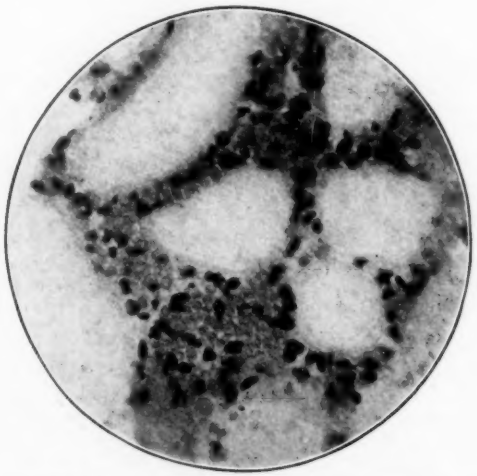

FIG. 3.—Animal experiment 11-56. Left ureter ligated for twenty-four hours. Shows necrotic epithelium of convoluted tubules surrounded by zone of active inflammation.

TABLE I.—Animal Experiment 11-58.

No of sample.	Date.	Quantity c.c.	Nitrogen per c.c.	Total nitrogen in 24 hours.	Albumin.
...	October 18	0	0	0	
157	October 19	170[a]	0.01084	1.842	+
...	October 20	0	0	0	
164	October 21	85	0.01554	1.320	+
...	October 22	0	0	0	
169	October 23	150	0.008405	1.260	+
...	October 24	21	0	0	
179	October 25	75	0.006818	0.511	
...	October 26	0	0	0	
189	October 31	65	0.01322	0.859	+
..	November 1	0	0	0	
196	November 2	95	0.012049	1.144	+
201	November 3	80	0.008728	0.698	
207	November 4	90	0.008817	0.783	
212	November 8	70	0.009796	0.685	+

Average nitrogen per day before operation, = 0.539. Average nitrogen per day after removing ligature, both kidneys secreting, = 0.637. Nitrogen from ligated kidney after removing right kidney as above.

Left ureter ligated October 9; ligature removed October 10; right kidney removed October 18.

[a] The full capacity of the bladder was 45 c.c. at autopsy.

TABLE II.—Animal Experiment 11–62.

Average nitrogen per day before operation, = 0.396. Average nitrogen per day from ligated kidney, = 0.350. Left ureter ligated October 11; ligature removed October 17; right kidney removed October 24.

The kidney that had been ligated for six days (see Table II, Animal Experiment, 11–62), after a reasonable length of time, was capable of excreting urine containing an amount of nitrogen compatible with nitrogenous equilibrium, while the kidney that had been ligated for twenty-four days (see Table III, Animal Experiment, 11–64), at first was able to excrete almost nothing at all. Subsequently, it partially regained its functioning capacity and at a later date almost entirely lost that capacity.

TABLE III.—Animal Experiment 11-64.

No. of sample.	Date.	Quantity c.c.	Nitrogen per c.c.	Total nitrogen in 24 hours.	Albumin.
249	November 30	15	0.00788	0.118	
250	December 1	55	0.00606	0.333	
251	December 2	87	0.00523	0.455	+
252	December 4	345	0.00066	0.227	
253	December 6	300	0.00077	0.231	

Average nitrogen per day before operation, = 0.680. Average nitrogen per day from right kidney, = 0.490. Average nitrogen per day from ligated kidney as above. Average from December 15 to December 26 = 0.303. Weight constant.

Left ureter ligated November 6; ligature removed November 29; right kidney removed November 29.

The urinalyses in general confirm the histological pictures.

3. Permanent lesions left after removal of the ligature. In the first example the ureter was ligated for twenty-four hours, the ligature then removed, and after eight days the unoperated kidney was removed. The animal was killed at the expiration of forty-four days after the first experiment. The ligatured kidney is larger than normal. Some slight gross evidence of connective tissue can be seen. Aside from a few hemorrhagic spots in the cortex and the slightly thickened medulla, nothing else is of interest. Under the microscope scattered areas of connective tissue and round-cell infiltration are occasionally encountered. The animal whose ureter had been ligated for six days, ligature then removed, and after another six days the unoperated kidney removed, was killed at the end of seventy-four days after the first operation. The following conditions were noted at autopsy: The operated kidney is large and there remains some evidence of former hydronephrosis. The tubules are still somewhat deformed, and the epithelium lining these tubules has an abnormal appearance. Scattered areas of connective tissue also occur. The permanent results of twenty-four days' ligation of the ureter is shown in Animal Experiment, 11–86. In this the ureter was tied for twenty-four days, when the ligature was removed and a nephrectomy done

at the same time on the opposite kidney. The animal was killed after thirty-seven days more. "The operated kidney is pale and shows areas of scar tissue on the cut surface, and retraction on the

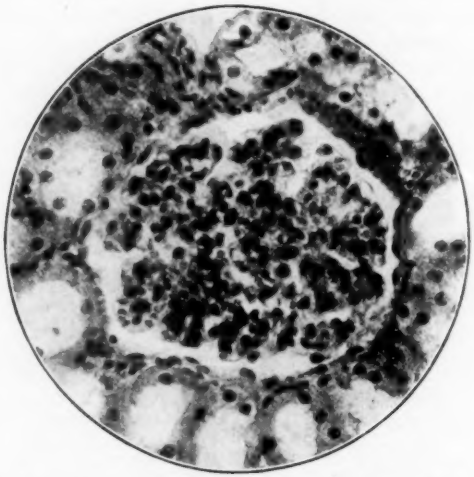

FIG. 4.—Animal experiment 11-56. Left ureter ligated for twenty-four hours. Shows glomerulus compressed; capsule surrounded by zone of congestion; dilated convoluted tubules with slightly compressed epithelium.

FIG. 5.—Animal experiment 11-61. Left ureter ligated for twenty-six days. Operated kidney; shows large areas of scar tissue incorporating remains of glomeruli and convoluted tubules.

outer surface. There are some remains of old hydronephrosis. There are ome wedges of connective tissue incorporating remains of convoluted tubules. The urine from this animal contains casts and albumin."

In Animal Experiment, 11–64, the ureter was ligated for twenty-three days, when the ligature was removed together with the unoperated kidney. The animal was killed at the end of fifty-five days. The operated kidney in this animal presented the same areas of scar tissue and round-celled infiltration incorporating epithelial remains.

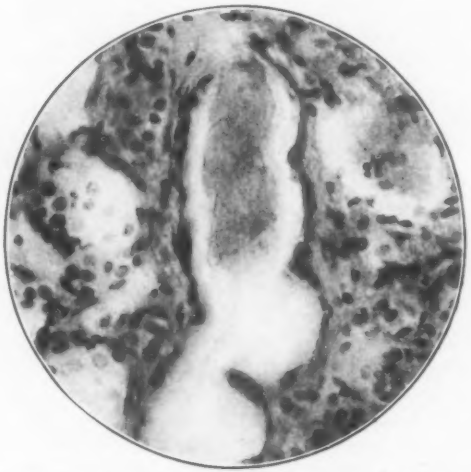

FIG. 6.—Animal experiment 11-61. Left ureter ligated for twenty-six days. Shows convoluted tubule with altered epithelium and remains of cast; also new connective tissue and round cells.

4. Changes in the unoperated kidney. It is with considerable hesitation that the author undertakes to describe the changes aside from those of compensatory hypertrophy in the unoperated kidney. These changes occur sometimes not at all and always at very irregular intervals. As has been predicated in the beginning of this paper, various authors have considered that the changes in the unoperated side were due to substances absorbed from the pelvis of the operated side, and that these substances are somewhat nephrotoxic. For this reason I have taken the contents of these hydronephrotic kidneys obtained after various periods of time, and injected them into normal rabbits. No ill effects in these animals was noted except that following the injection of the fluid there seemed to be a decrease in the amount of nitrogen excreted. At autopsy at the end of twenty-four hours, the kidneys of 2 of

these animals presented some slight pictures of congestion. In one instance the unoperated kidney presented only evidence of compensatory hypertrophy, and the fluid from the operated side had no nephrotoxic properties whatever.

If we exclude such changes as slight dilatation of the tubules and fragmentation of the protoplasm of the cells due to artefacts, no important lesions occurred in the non-operated side of the one day or the six day rabbits. In 2 of the animals in which one ureter had been ligated for a period of twenty-three days, there occurred more or less change in the unoperated kidney. We can absolutely, I believe, exclude the question of changes antedating the operation, by the fact that all of these rabbits had very careful quantitative urine analyses made for a period of several days before operation. Those presenting any anomalies in the urine were rejected for operation.

The changes in the unoperated kidneys of the twenty-four day rabbits did not seem to bear any definite relation to each other, and varied from the occurrence of a few hyaline and epithelial casts to a condition of round-cell infiltration, and even scar tissue production. In cases where nitrogen determinations were made of the urine from the unoperated side, it was frequently found that there was an increase of nitrogen and usually some albumin (see Table IV, Animal Experiment, 11–61). This oftentimes persisted for a longer period of time than could any immediate effect of the anesthetic have lasted. In 2 animals only compensatory hypertrophy occurred in the control kidney.

TABLE IV.—Animal Experiment 11–61.

Average nitrogen per day before operation, = 0.566. From October 12 to October 26 variable. Average nitrogen per day from non-ligated kidney, = 0.693. Ureter ligated October 11. Animal killed November 6.

CONCLUSIONS. At the commencement of this work, the author hoped to be able to tell in a single word whether or not it would always be necessary to remove a kidney having an atresia of the ureter from any cause. He soon found that the answer must be as ambiguous as that of the Delphic oracle, for the results of atresia of the ureter do not always seem to be the same. However, these facts remain: There almost always results severe destruction of the kidney after prolonged obstruction. To save anywhere near the full functional capacity of the kidney, the obstruction must be removed not later than six to ten days. Beyond twenty-four days the removal of the kidney seems justifiable on the following grounds:

1. There remains but little functionating kidney.
2. Hydronephrosis is a common result of atresia of the ureter. The existence of hydronephrosis is always a potential danger.

These sacs frequently mechanically cause disturbance and if one is infected it may become a veritable Vesuvius.

3. In some cases there occur changes in the unoperated kidney and we are led to assume that these changes result from the presence of the no longer functioning kidney. Whether infection of the hydronephrotic fluid by low grade bacteria is the cause of these unoperated kidney changes, does not alter the conclusion.

ADDITIONAL REFERENCES.

P. A. Lewis. Jour. Med. Research, xvii, 291.
E. H. Fenwick. Trans. Path. Soc., London, xxxvii, 300.
T. G. Brodie. Jour. Phy., xxxiv, 225.
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CLINICAL MANIFESTATIONS OF ILLUMINATING GAS POISONING.[1]

By Robert S. McCombs, M.D.,

ASSOCIATE IN MEDICINE, PHILADELPHIA POLYCLINIC AND ASSISTANT PHYSICIAN TO THE CHILDREN'S HOSPITAL, PHILADELPHIA.

During the last ten years I have had the opportunity to observe 1000 cases of illuminating gas poisoning in several cities through connection with the medical staffs of several of the large gas companies of the United States. Many of the cases observed have been repeatedly examined, some over a period as long as two years. The employees of the companies in the large gas generating plants, and members of the street gangs, who come more in contact with illuminating gas than others, have been under direct observation throughout these years. During this time some of the men have been overcome fifteen or twenty times, and this has given the opportunity to study the so-called cases of chronic gas poisoning.

It is obviously impossible in the limits of this paper to note the full classification of symptoms and actual statistics of my studies. I will, however, give a complete summary of the results based upon studies of the records and personal observations.

Physiological chemistry: The toxic action of illuminating gas has been fully described by such authors as Sellman,[2] Haldane,[3] Edsall,[4] Crile and Lenhart.[5] To summarize:

In illuminating gas, as furnished by the better companies, the carbon monoxid present is the poisonous principle, the other constituents used to increase the candle power are non-toxic. Carbon

[1] Read by invitation, before the College of Physicians of Philadelphia, May 1, 1912.
[2] Pharmacology.
[3] Hale White's Pharmacology.
[4] Osler's Modern Medicine, vol. vii.
[5] Amer. Jour. Med. Sci., October, 1907.

monoxid has an affinity for hemoglobin three hundred times greater than oxygen; it excludes the oxygen; the resulting compound is not perfectly stable so that when oxygen is present in very great excess the carbon monoxid hemoglobin will be decomposed and oxyhemoglobin formed. While oxygen cannot directly displace the carbon monoxid, it has been established that dissociation of the carbon monoxid hemoglobin occurs under these circumstances, and that the carbon monoxid is expired as such, no noteworthy amount being oxidized into carbon dioxid. At death as much as 60 to 80 per cent. of the hemoglobin in the circulation will be in combination with carbon monoxid. The resultant symptoms are due principally to a diminution of the supply of oxygen to the tissues of the body. There is also a direct toxic action in the human being. At first there is a stimulation of the central nervous system, followed by paralysis, the order being brain, spinal cord, and medulla. There have been several instances in which plants have been destroyed by gas.

For purposes of convenience the various symptoms of illuminating gas poisoning have been divided into three stages, this is my own classification, conceived with the idea of giving employees definite divisions for the application of first aid methods.

Symptoms. The first stage continues until the patient looses consciousness. During this period the following symptoms will develop: Cerebral excitement and dilatation of the cutaneous vessels, occasionally cyanosis will be noted if the poisoning is very acute, the venous blood being practically free from carbon monoxid; dizziness; headache; pains in the extremities; muscular twitchings slow pulse from stimulation of the pneumogastric; rise in blood pressure from stimulation of the vasomotors; there is a feeling of constriction of the chest, rarely actual dyspnea; wide dilatation of the pupil; nausea and vomiting. Late in this stage there is a feeling of general weakness, faintness, languor, and at times, stupor. Some times there is delirium. The temperature is normal or slightly elevated.

The second stage begins with syncope and ends with apnea. The patient is unconscious but breathing, the respirations are rapid and stertorous with a corresponding increase in the pulse; the blood pressure falls; the temperature is elevated, at times reaching degrees of hyperpyrexia; there may be loss of sphincter control and of some of the reflexes, although these are not constant. At times there are general tetaniform convulsions. Some cases show only a profound state of coma without the above-mentioned symptoms, one case I saw in consultation had persisted for nine days, this man had not been properly treated according to our present knowledge. Toward the end of the second stage there is general muscular rigidity and a weak rapid pulse at times as high as two hundred; the jaws may be stiff and the tongue swollen; the peculiar cherry-red markings, so characteristic after death,

may make their appearance on the skin of the neck, trunk, and thighs. The spectroscope will show the presence of carbon monoxid in the blood. The respirations gradually become weaker until there is apnea.

In the third stage the patient is comatose and respirations have ceased. A very rapid, weak, intermittent heart action is all that indicates the presence of life. All symptoms of asphyxiation are present except cyanosis, which is absent unless poisoning has been very sudden. In the slower, gradual poisoning we may find the cherry-red markings of the skin. The presence of carbon monoxid in the blood may be determined by the spectroscope. The muscular rigidity before mentioned may be present.

DEATH. If the skin surface is not discolored at death, within an hour or two it will become deeply marked especially in the dependent parts with cherry-red areas. Likewise, the toes will become fully extended and the hands assume the tetany position. This extension of the toes and fingers seems to appear after death earlier in children than in adults. At postmortem examination the organs are deeply injected, especially the spleen, there may be scattered small hemorrhages and at times cerebral changes, particularly areas of softening in the lenticular nucleus, symmetrical in many cases. (Spiller.) The blood is pink in dilute solutions and shows the presence of carbon monoxid by the spectroscope.

The test suggested by Hoppe-Seyler—namely, that blood containing carbon monoxid treated with double its volume of a solution of sodium hydrate yields a beautiful red color when spread on a porcelain plate, while ordinary blood under the same conditions is changed into a dirty brownish mass, which exhibits a trace of green—has not given satisfactory results.

A fairly accurate test is the action of the blood when it comes in contact with the atmosphere, if it immediately turns scarlet carbon monoxid is probably not present to any great extent as its presence retards the formation of oxyhemoglobin. The spectroscope, however, is the most accurate method.

The length of time necessary for a person to pass from one stage into the other is uncertain, two factors determine this, (1) the amount of gas inhaled, and (2) the personal idiosyncrasy. Under ordinary conditions a man can breathe a high degree of carbon monoxid for two minutes without symptoms, some of the men can stand it for five minutes. There are some exceptions to this rule, I have seen men pass almost immediately from the first into the third stage after inhaling a small quantity of gas. One can never be sure that an individual who is apparently only slightly affected will not pass into the second or third stage very suddenly and without premonitory symptoms, this is not common, but a person suffering from the effects of gas should be constantly watched.

Another phase is shown by the following: A young colored girl

who had been exposed to a mild degree of carbon monoxid, and apparently had no symptoms whatsoever, at the end of twenty-four hours developed stupor, severe pains in her extremities, and a temperature of 102° F. In the meantime she had not been within several blocks of the leaking gas. These cases are the exception not the rule. If a patient is breathing well when rescued the test for carbon monoxid is hard to get after three hours and the danger of direct death from the immediate poisoning is over in about one hour. When respirations are shallow the time is lengthened.

SEQUELS. Symptoms that persist after the blood is free of carbon monoxid are referable principally to the nervous system. They include neuralgia, nervousness, insomnia, pain, intention tremors, loss of sexual power, loss of continuity of thought, delirium, confusional insanity, transient hemiplegia, glycosuria, and prolonged fever. There have been cases of bronchopneumonia. I have not seen any cases of multiple sclerosis, ocular changes, nystagmus, paralysis of the recti, protrusion of the eyeball, hemianopsia, nor gangrene which have been reported. All of the sequels mentioned have eventually cleared up entirely within a period of six months or less. They constitute less than 2 per cent. of all the cases and are almost entirely confined to advanced second stage cases and third stage cases. Any method which tends to shorten the period during which the blood is impaired will tend to prevent the late symptoms due to tissue injury. There have been individuals poisoned by illuminating gas who have been suffering at the time from chronic organic involvements of almost every description, many pregnant women are included in these statistics, also patients with tuberculosis and several who were in the midst of typhoid fever. None suffered any permanent bad effects and no miscarriages have occurred; the children when born have been normal. Sequels are more likely to occur in those of advanced years.

PROPHYLAXIS. It is not the purpose of this paper to belittle the poisonous nature of carbon monoxid. The fact remains, however, that deaths result in nearly all cases from preventable causes.

It should be noted in comparing this statement with various reports of accidental deaths from carbon monoxid poisoning, which amounted to 624 in twenty-three years in the State of Massachusetts, as reported by Sedgwick and Schneider, that the cases may be divided very sharply into two classes of accidental poisoning.

1. Those in which the accident consists in a direct break in a pipe in a room; failure to close the gas jet (the usual method); or by other accidental causes of a similar nature, all of which produce contamination of the atmosphere with a high degree of carbon monoxid in a short time.

2. Accidental cases due to street leaks; due to cracking of the

mains by frost, the unequal contraction of frozen ground will break the pipes. At times the escaping gas cannot filter through the superimposed earth, but works its way through water and rat holes or along pipes into the cellars. The odor of gas is always noticeable. In Philadelphia there has been only one instance where death has resulted from the second class of cases and this was preventable.

Suicidal cases make up approximately one-half of all the fatalities here and in Massachusetts.

The majority of deaths were preventable if the individuals had slept with open windows, had paid attention to leaking gas and had reported it immediately, and of course, if they had properly closed the gas stop.

TREATMENT. The essential of treatment consists in the inhalation of oxygen, under pressure whenever possible. The object of all plans of treatment is to supply oxygen in sufficient quantities to displace the carbon monoxid in combination with the hemoglobin.

Oxygen inhalations are indicated in all stages.

In first stage cases fresh air combined with mild stimulation, such as aromatic spirits of ammonia, should be administered. In this stage the nausea, vomiting, and headache are the most troublesome symptoms. The greater part of the gastric symptoms will be relieved by some effervescing salt, the patients feeling much better after eructating or vomiting. It is due to this relief from nausea and gastric distention that a peculiar remedy for gas poisoning obtained its reputation as an antidote among men working in gas; it is an effervescing birch beer, called "Weiss Beer." Effervescing phosphate of soda has been substituted. There is no true antidote for gas poisoning other than oxygen. The headache usually persists for twenty-four or forty-eight hours and may be relieved by any of the drugs used for this condition. Violent exertion is to be avoided, as collapse is a danger; men who have become aggressively delirious have collapsed.

Second stage. The patient is unconscious but breathing. It may be necessary if the respirations are not stertorous to assist the respiratory action. The Howard method (compression of the lower part of the chest in rhythm with expiration) has been found efficient. Oxygen must be administered preferably under pressure. Haldane placed animals (mice) in oxygen under a pressure of two atmospheres, so that simple solution of oxygen in the blood serum was obtained sufficient to support life independently of the hemoglobin. Enough carbon monoxid was present to completely saturate their hemoglobin. Under these conditions the animals remained normal as to symptoms, showing that the carbon monoxid had no direct toxic action. When the pressure was removed and the mice put out in the air they died with symptoms of asphyxia.

Various mechanical devices for administering artificial respiration and supplying oxygen have been tried but until lately all were unsatisfactory. At present the "pulmotor"[6] is being used. This machine automatically adjusts itself to the individual capacity of the lungs, without danger of rupture, and maintains a mixture of oxygen and air (60 per cent. oxygen) under a constant pressure of five atmospheres. It maintains artificial respiration perfectly. Reports from all over the country relative to its efficiency have been received. Whenever possible it should be used. Undoubtedly the prompt suction by the "pulmotor," of the carbon monoxid present in the residual air and that which is being constantly eliminated from the blood, materially aids resuscitation.

Medicinally the patient should be freely given hypodermics of stimulants such as camphor, caffeine, digitalis, and strychnine. Heat should be applied when indicated and as there are several cases in which the persons have collapsed when taken out into cold air, it is always better to start treatment in a warm room. A very important adjunct to this plan of treatment is the massaging of the muscles after aerating the lungs, the increase in the hemoglobin in the general circulation accomplished by it often promptly restores the normal oxygen balance.

The above methods are usually followed by prompt recovery. If they are not successful, venesection with the introduction of normal salt solution should be employed. Two cases have come under my personal observation at the Philadelphia Polyclinic Hospital in which this method was followed by rapid and complete recovery, although there was some mental confusion in both cases for some time. Favorable reports of cases treated by this method are made by Jersey, Wilkie, Schruber, and von Gordon, 8 in all, and including the 2 mentioned above making 10. Crile and Lenhart[7] report 5 deaths at the Cook County Hospital, Chicago in which this method was employed. I believe it should be employed when the patients are in fairly good condition when rescued, that is, a fair pulse, stertorous respirations, unconscious, and with no immediate signs of collapse. However, the "pulmotor" has made its necessity less frequent. Venesection and transfusion of defibrinated blood was practised by some clinicians in the seventies, those for and against this method were about equally divided. Should the "pulmotor" fail, the best method is the direct transfusion of blood as practised by Crile and his followers. His experiments, reported in the AMER. JOUR. MED. SCI., led him to conclude that blood transfusion seems to be of greater therapeutic worth than the other measures considered. It has been used in 2 cases in Philadelphia, both of which made a prompt recovery after other

[6] The pulmotor is manufactured by the Draeger Oxygen Apparatus Co., Pittsburg, Pa.
[7] Loc. cit.

methods had failed. The introduction of fresh hemoglobin which will combine with oxygen and which will not be contaminated by the carbon monoxid already held in a combination with the patient's hemoglobin is a sure way of restoring the normal oxygen balance. Transfusion should be done immediately if the patient is in the advanced second or in the third stage and fails to respond to the ordinary treatment. The only objection to this plan of treatment, according to Dorrence, is the fact that about 25 per cent. of transfusion operations are failures unless undertaken by skilled surgeons.

Third stage. The patient is not breathing and is unconscious. Artificial respiration, oxygen, stimulation and heat are imperative. Transfusion is indicated. The Schafer or "prone pressure," method of artificial respiration is the best to use. The "pulmotor" has maintained artificial respiration in this stage.

Artificial respiration has been maintained for six hours with subsequent recovery of the patient.

Prognosis. If the above methods of treatment are carried out and the patient is not dead when discovered practically all cases should recover in forty-eight to seventy-two hours from the immediate effects of the gas, no matter how concentrated the carbon monoxid causing the poisoning. The great difficulty in treatment has been the failure of both laity and physicians to realize that inhalation of oxygen under pressure combined with venesection or blood transfusion in severe poisoning will save practically all the cases.

Of 39 cases reported by Edsall[8] occurring at the Episcopal Hospital in Philadelphia, mostly suicidal in intention, 34 fully recovered and most of the fatalities were due to sequels.

The possibility of sequels developing sometime after the poisoning must be borne in mind, but all such cases in my experience have cleared up within six months.

Gilman Thompson[9] considers it a bad sign if leukocytosis, which he says is usually present, be of a high degree.

Chronic Gas Poisoning. Examinations of the blood of men who are constantly in contact with carbon monoxid, and of some who have been repeatedly poisoned, have been made. The average count shows a polycythemia. This is in accord with the report of the investigating committee authorized by the Illinois Legislature and published in the *Journal of the American Medical Association*, also with the 2 cases reported by Reinhold.[10]

I could not find any muscular weakness in the men examined. Some of them had been employed in this line of work for twenty years and are now among the strongest and healthiest individuals I know. As a rule, they pay no more attention to first-stage gas

[8] Loc. cit.
[9] Cited by Edsall.
[10] Ibid.

poisoning than the average person would to a headache. The estimation of muscular weakness by comparison with men in other occupations is difficult to obtain and is unreliable at best.

I have seen no accumulative action of carbon monoxid unless the polycythemia may be an evidence of it. Reported symptoms such as irregularity of the heart, slow pulse, anemia, lack of concentration, poor memory, cardiac dilatation, splenic enlargement, and pleural effusions have not been observed in the laboring class I have had under observation.[11]

Evidently the increase in the red blood corpuscles, the polycythemia, is to compensate for the presence of small quantities of carbon monoxid so that the normal supply of oxygen to the tissues can be maintained.

[11] I think illuminating gas is blamed for a large number of cases of serious chronic poisoning which are due to defective heating apparatus and to broken furnace pots.

REVIEWS

SURGICAL OPERATIONS. A HAND-BOOK FOR STUDENTS AND PRACTITIONERS. By PROFESSOR FRIEDRICH PELS-LEUSDEN, Chief Surgeon to the University Surgical Clinic and Chief of the University Surgical Polyclinic in the Royal Charity Hospital of Berlin. Only authorized English translation; by FAXTON E. GARDNER, M.D., New York. Pp. 726; 668 illustrations. New York: Rebman Company.

PROFESSOR PELS-LEUSDEN has taught operative surgery for many years, and, as he states in his preface, the present book is born from a desire to link together what he has long taught in practical courses and theoretical lectures. Like many writers he addresses his book to students and general practitioners, and modestly adds that he will feel gratified if the *specialist*, by which term it is presumed he means the accomplished surgeon, shall find therein anything useful.

The operations of surgery are discussed regionally: Extremities, head, neck, thorax, abdomen, and genito-urinary organs. Operations on the female genitalia are not included. But before this regional portion of the work there are important chapters on antisepsis and asepsis, anesthesia, division and reunion of the different tissues, and surgery of the bloodvessels.

There is much in this volume that is unfamiliar to the majority of surgeons not thoroughly informed of current German teaching; but surgeons of other nationalities, especially American surgeons, will look in vain for many procedures that to them are operations of routine. An American operation that is twenty, or at the least, ten years old, finds its place in this volume and is described as a novelty. There is nothing described so modern as endo-aneurysmorrhaphy. The V-shaped excision of the lower lip is described as if no better plan could be desired. There is no mention of Dowd's transverse cervical incisions for extirpation of lymph nodes. The muscle-splitting incision for exposure of the appendix is described, but it is not distinguished by McBurney's name; while Lennander's name is given to the incision previously described by Battle, by Kammerer, and by Jalaguier, none of them, surgeons practising in Germany. A "complicated" method of operation for the radical cure of umbilical hernia is quoted from Graser, as if the writer

himself had no familiarity with it; and in parenthesis he mentions that Graser says the method of suture had been used before in similar cases by Girard, Mayo, Baracz, and others. This is the only description of the "Mayo" operation, which in this country is thought both useful and sufficiently simple of execution. There is no mention of Ruggi's inguinal method in operations for femoral hernia.

On the other hand, as stated above, there is a great deal that might well be adopted in this country, as well probably as in Great Britain. Especially worthy of note is the extent to which local anesthesia is employed by the German surgeons. Though it is certain that operations on phlegmatic Germans may be more easily conducted without the influence of a general anesthetic than those on more sensitive individuals, it is equally true that many more operations in this country could be successfully performed under local anesthesia than the average surgeon here realizes. The operation must be conducted more slowly, and the manipulations must be immeasurably more gentle; but in certain classes of cases the results are worth all the trouble that the method entails; and nowhere can the operator learn the method better than from this book.

Another instance of progressiveness in German surgery is the apparent freedom with which the brain is explored. Nothing sounds more simple than to spray the scalp at the desired point with ethyl chloride; then to bore through the skull with a gimlet driven by electricity or by hand; and finally, to insert a long hypodermic needle through this hole and explore the brain by creating negative pressure in the barrel of the syringe. The only question that comes to the mind of a practical American surgeon after reading the description will be "what will I learn even if I get some fluid or particles of brain substance?"

So, under "Trephining," Pels-Leusden says "in former times we used the so-called trephine." Nothing so old-fashioned is recommended today; only bits and braces and Gigli saws and Dahlgren forceps are advised, apparently forgetting that bits and braces, in the form of the old "trepan" long preceded the "so-called trephine." Cushing's subtemporal decompression is mentioned, doubtless because his early brain surgery was done with Kocher; if it had been purely American bred next to nothing would be known of it in Germany. Thus there is no mention of the Spiller-Frazier operation for trigeminal neuralgia.

The illustrations are not beautiful, but show what the author wishes. Almost all are diagrams. The student will profit by this as well as by the attention paid to the details of the operations described, and to the preparation and after-care of the patient. The reasons for the various recommendations are given, and thus the author's advice is more easily remembered. The important

place given to applied anatomy in the descriptions of operations is characteristic of a careful and successful operator.

The translator has done his task well, preserving the German idiom, and using an abundant number of Anglo-Saxon words, which render the text altogether delightful and refreshing.

Comparisions are odious; but this volume naturally lends itself to comparison with Kocher's Operative Surgery, which through the excellent translation of Mr. Stiles is more familiar to English reading surgeons than any other work of the kind by a foreign author. The work of Prof. Pels-Leusden of course does not enjoy the great prestige which attaches to a text-book from the pen of the Prophet of Berne; he is content to take operative procedures as he finds them, and does not convert others' methods into original operations by the mere process of absorption. There is an old saying whose truth always seems challenged when a text-book by Kocher is consulted. This is the saying that the originality of most men consists in their ignorance of the work of others. Kocher cannot be charged with ignorance of anything in surgery; yet almost all his operations are described as original with himself. This is not the case with Pels-Leusdon. The two text-books cover about the same ground, though Kocher's has grown to an immense size in its later editions. Pels-Leusden will do well if he can preserve the present athletic figure of this child of his brain when it has reached middle life. *Μέγα βιβλίον μέγα κακόν.*

A. P. C. A.

SERUM DIAGNOSIS OF SYPHILIS. By HIDEYO NOGUCHI, M.D., M.Sc., Associate Member of the Rockefeller Institute for Medical Research, New York. Second edition; pp. 238; 14 illustrations. Philadelphia and London: J. B. Lippincott Company.

THIS book was the first English effort to put in simple and adequate form the principles of hemolysis and the technique of the Wassermann reaction. It gave in a clear-cut manner the gist of an enormous literature and the results of Dr. Noguchi's own researches. The second edition amplifies these principles by describing each factor with their intimate quantitative relations, their meaning, significance, and the sources of error. He shows the necessity for a quantitative control of every factor. The need of fixed standards of practical constancy, and the means of arriving at those constants, he emphasizes and carefully describes. Reviewing the original Wassermann reaction and the more prominent modifications, he briefly classifies them according to the hemolytic system used and the source of the complement, pointing out in every case the possibilities of error. The preparation of the reagents, the technique of the Wassermann reaction, and of

his own modification, and the methods of standardizing each factor of the test and of quantitatively estimating the antibody content of a serum by a titration of the diagnostic dose are described and made clear by charts. Each possible error is now considered and the means of discovering and correcting it described. The quantitative changes due to inactivation were experimentally studied and a curve of gradually decreasing antibody content plotted out.

The later chapters condense much literature into tables made up of cases from all stages of syphilis, of conditions where syphilis is of possible etiological importance, and of controls from practically all fields of medicine. The cases are tested with Wassermann or Noguchi reaction or both. Some few studies were made upon the effect of treatment with mercury or "606." In these last cases the actual number of syphilitic antibodies were determined before and after the injection. In every case a diminution of antibody content was demonstrable by titration, but in many cases not seen with the diagnostic test.

The technique of the butyric-acid test, both for blood and spinal fluid is included, noting the parallelism to cell count in cases of parasyphilitic disease. This has considerable value in psychiatry although not specific for syphilis.

The book ends with a glossary for all the new terms and a rather full bibliography. It amply fulfills the idea of Dr. Noguchi for a serviceable laboratory book and gives enough clinical data to make it interesting also to the internist.

The book is primarily concerned with Dr. Noguchi's methods and does not give quite as much prominence to the Wassermann reaction itself which is still, today, the more popular reaction.

E. P. C. W.

THE SURGICAL CLINICS OF JOHN B. MURPHY, M.D., AT MERCY HOSPITAL, CHICAGO. Vol. I, No. 3. Pp. 174; 61 illustrations. Philadelphia and London: W. B. Saunders Company, June, 1912.

THE June number of the *Murphy Clinics* contains, as have the previous issues, clinical lectures on various subjects of modern interest. Surgery of the bones and joints, of the nerves, tuberculosis of the peritoneum, cystic goitre, hypernephroma, cholelithiasis—these are the topics which are discussed at greatest length. Of special interest are the numerous skiagraphs showing the condition of the bones before and after operation in many different cases. The results of arthroplasties of the hip and knee are shown, and the extent of function which is regained by the patients is demonstrated by photographs, and is sufficient evidence of the success of the operative technique.

Then there is a case of rupture of the brachial plexus which is of much interest, though as usual the reader derives more information from the reasoning by means of which a correct diagnosis is reached than from the details of operative technique which are clouded rather than clarified by the stenographic report of Dr. Murphy's remarks during the performance of the operation.

Several of Dr. Murphy's clinical lectures are further elucidated by comments by specialists who have been called in consultation. Thus Dr. Richard J. Tivnen discusses the laryngological aspects of goitre; Dr. Bransford Lewis speaks on the diagnosis of kidney lesions in connection with the case of hypernephroma; and Dr. Charles L. Mix makes some remarks concerning "typhoid spine," though the diagnosis in the present instance does not seem very positive. Dr. Mix also discusses the symptoms presented by the patient who was operated on after a diagnosis of Extradural Hemorrhage from Trauma; this patient had been injured twelve years previously, and the operation was undertaken to relieve progressive mental deterioration, with spastic hemiplegia. The treatment consisted in excision of the dura which overlay the diseased Rolandic region of the cerebrum, and replacement of the osteoplastic flap. Incidentally, Dr. Murphy recommends ligation of the external carotid as the best treatment for rupture of the middle meningeal artery.

The "Five Diagnostic Methods of John B. Murphy," which are inserted at the end of this number of the *Clinics*, are reprinted from an article published in 1910 by Dr. Guy G. Dowdall, and therefore are the "exception which proves the rule" laid down so often by the publishers in their italicized advertisements that "everthing is new, never having appeared in print before."

A. P. C. A.

NEPHRITIS. AN EXPERIMENTAL AND CRITICAL STUDY OF ITS NATURE, CAUSE, AND THE PRINCIPLES OF ITS RELIEF. By Dr. MARTIN H. FISCHER, Eichberg Professor of Physiology in the University of Cincinnati. The 1911 Cartwright Prize Essay of the Association of the Alumni of the College of Physicians and Surgeons, Medical Department of Columbia University, New York. Pp. 203; 30 illustrations. New York: John Wiley & Sons, 1912.

A REVIEW of this book must take into consideration, the fact that there is here advocated an iconoclastic theory quite at variance with our preconceived notions and almost opposite to the therapy of today. Lacking data by which to judge it, however probable or improbable its tenets may appear, finality of opinion should be reserved.

To his own satisfaction at least, Dr. Fischer has reduced the complicated and antagonistic phenomena of nephritis to a basis so simple as to suggest that such an hypothesis should have been offered and tested ere this. On page 2 of his book, Dr. Fischer, for the sake of clarity in argument anticipates his general conclusions as follows:

"All the changes that characterize nephritis are due to a common cause—the abnormal production or accumulation of acid in the cells of the kidney. To the action of this acid on the colliodal structures that make up the kidney are due the albuminuria, the specific morphological changes noted in the kidneys, the associated production of casts, the quantitative variations in the amount of urine secreted, the quantitative variations in the amounts of dissolved substances secreted, etc."

At last analysis, Dr. Fischer's evidence for this view consists very largely of analogies drawn from the behavior of gelatin and fibrin. When placed in fluid media of various reactions, and in proportion as they swell or dissolve or are influenced by salts present and so on, he feels justified in deducing a similar behavior on the part of the kidney. That this is an entirely sound method of reasoning and that the conclusions so reached are dependable, is open, of course, to question and indeed were it not that Dr. Fischer cites experiments on animals in which nephritis is induced and alleviated and experiments on humans in which the symptoms of nephritis are relieved or dissipated, one could disregard much of the argument. Dr. Fischer's analogies may be correct, but they serve to illustrate his hypothesis and not to prove it.

The experiments *in vivo*, however, in which he applies the simplest of measures as causative and curative, must be taken, on their face value, as remarkable and mark, if true, a long step in the solution of these conditions. Their repetition and acceptance by other workers must be awaited with interest.

In justice to Dr. Fischer, it must be candidly said, that should he prove correct in even a part of what he advocates, as is not inconceivable, he will deserve well, and it is further to be borne in mind that this may prove not the first instance in medicine where the forest has been hidden by the trees. Dr. Fischer has a faculty of turning the experimental data of others to his own account. even when advanced in seeming contradiction of his own views, but he has at least the courage of his convictions and does not hesitate to postulate in this difficult field where any radical move is sure to encounter opposition.

The author has a rather commendable clarity and vigor of style which make the text easy reading and the English is sufficiently within the bounds of good usage to pass muster.

The illustrations, which are quite numerous, are in large part photographic reproductions, and the publisher's work in general has been well done. R. P.

DIE ERKENNUNG DER PSYCHOPATHISCHEN KONATITUTIONEN (KRANKHAFTEN SEELISCHEN VERANLAGUNGEN) UND DIE ÖFFENTLICHE FÜRSORGE FÜR PSYCHOPATHISCH VERANLAGTE KINDER. By PROFESSOR DR. TH. ZIEHEN, Geh. Med., Rat Direktor der Psychiatrischen und Nervenklinik der Kgl. Charite in Berlin. Pp. 34. Berlin: S. Karger, 1912.

THIS little paper of 34 pages should be translated into English and distributed among all intelligent men and women, for it applies as well to American as German social conditions. It deals with that class of psychopathic children in which are included not the idiots, imbeciles, feeble-minded, or insane, but those children who are morally weak and who sooner or later come within the pale of the law. Such children may have bad heredity, some injury at birth with possible concussion of the brain, early use of alcohol, or some infectious disease which has caused encephalitis. At any rate, these are the children who early in life begin to steal and lie, learn slowly, and for one reason or another are called bad by their parents and teachers, and who sooner or later come under the influence of the law. As boys or young men they become thieves, and finally land in jail, while the girls become prostitutes. Professor Ziehen, and there is no one better qualified, discusses their ever-increasing number and deplores that there is so little done for them. Even in that land of progress there is no special school where these psychopaths can be placed, and this paper is really a plea for the establishment of such institutions.

The reviewer for many years has been called upon by the House of Detention of Philadelphia to examine the nervous and mental condition of children arrested for various causes. It has always been a question as to where to put these children. They are neither epileptic nor feeble-minded, and therefore cannot be put in such institutions. Private homes are not open to them, and therefore the only place left is the Home for Incorrigible Children, in which they learn many things they should not, and after a number of years in the majority of instances are worse off than when they first entered. Instead of building jails it would be vastly better if the State built training schools or camps in which such children could be properly educated and trained to be useful citizens and to have a proper respect for the law. What a vast saving it would be, after all, to the State if this were done, for it would save the expense of their trial and incarceration in jail, and what a great thing it would be for the children who are not to blame, for nearly always it is because they have not had the proper care or the environment to keep them from being criminals. What a curious law it is which should take care of the criminal, but which does nothing to prevent the criminal; and what a curious civilization it is which spends millions upon educating the savage, but nothing upon educating the children who live at its back doors. T. H. W.

GRUNDRISS DER HAMATOLOGISCHEN DIAGNOSTIK UND PRAKTISCHEN BLUTUNTERSUCHUNG; EIN LEITFADEN FÜR ANFANGER, STUDIERENDE UND PRAKTISCHE AERZTE. By A. PAPPENHEIM. Pp. 264; 8 colored plates. Leipsig: Klinkhardt.

ALTHOUGH covering 264 pages, many of which are in fine type, the author makes a point of the fact that his book is a "guide." The preface states that the work is founded on the author's course of lectures and that it is his intention to present the subject briefly, avoiding lengthy discussion of matters that still are in doubt and simply presenting those features of theoretical morphology and cytogenesis that are necessary for an understanding of clinical diagnosis. An introduction, eight pages in length, discusses splendidly the limitations of hematology and its relation to medicine in general. The author emphasizes the fact that the alterations of the blood are most frequently simply associated symptoms of a disease whose most striking effects are seen elsewhere than in the blood, and that diseases of the hematopoietic system and the blood itself form a very distinct minority of the conditions studied by hematologic methods.

The book is divided into two parts, the first dealing with hematology in its general and theoretical aspect, the second describing the technique of hematologic examinations. Thus, Part I takes up the chief cell types of normal blood and briefly states the most modern views as to their genesis. This is followed by a description of their pathological variations accompanied by sufficient discussion of hematogenesis to make clear the origin of the pathological types. Not only are variations in morphology discussed, but the quantitative relations of blood elements to one another in pathological states also are considered. Part I*a* deals with the theory and theoretical pathogenesis of anemias, leukocytoses, and leukemias in the order of the author's classification of these conditions. This is followed by a discussion of the worth of the various hematologic symptoms in the light of their pathogenesis, and the matter concluded with a discussion of the clinical interpretation of the information acquired by hematologic methods.

Part II, devoted to the actual technique of the blood examinations, describes in thirty-eight pages several methods of estimating the percentage of hemoglobin, counting the cells, and making stained preparations for differential counting. Following this and really in the form of an appendix to the book, are eight beautifully colored plates diagrammatically illustrating the blood pictures of several morbid conditions. Aside from these excellent plates the book is poorly illustrated, there being but a few wood cuts and diagrams which serve almost no purpose in clarifying the text or beautifying the book.

The book, as a whole, is poorly balanced, the theoretical dis-

cussion occupying a number of pages far in excess of the space devoted to technique, a feature that seems faulty in a work purporting to be a guide for beginners. The two parts taken individually show a fine sense of proportion, each subject being given an amount of consideration quite in ratio to its importance.

Throughout the book the most important points are printed in large type, features of especial interest being emphasized by the use of black-faced type. Detailed discussions and relatively unimportant points are printed in fine type, so that the hasty reader, omitting these parts, can get the substance of the writer's meaning by limiting himself to the reading in large type.

In criticism of Part II, on technique, it may be said that the brevity of presentation excludes from consideration numerous well-established and useful procedures, this being particularly true of the staining methods, in which field the author limits himself self to a description of his own modification of the combined May-Giemsa methods. If, however, the reader simply desires a series of dogmatic directions for making the essential determinations of the conditions of the blood, this part of the book will be found amply sufficient.

At the beginning of the book, there is found the usual "Inhaltsverzeichnis," but the work suffers considerably from the complete absence of an alphabetical index to its contents, a feature which would add much to the value of the book to the "beginner, student, or practising physician" who choses it as his "guide." H. T. K.

RECENT ADVANCES IN HEMATOLOGY. By WALTER K. HUNTER, M.D., D.Sc., Fellow of the Royal Faculty of Physicians and Surgeons: Lecturer and Examiner in Practice of Medicine. Glasgow University. Pp. 119; 1 colored plate. New York: William Wood & Co., 1912.

THE book consists of a series of three lectures, the Dr. James Watson Lectures for 1910 delivered before the Royal Faculty of Physicians and Surgeons of Glasgow. They originally appeared in one of the medical journals of Scotland, and although there evidently was a demand for them to appear in book form, the author apparently hesitated in bringing them out in a collected series, but later yielded to these demands. The advisability of this step cannot be questioned, as the author had compiled a thorough and complete book dealing with some of the recent advances in hematology.

Lecture I consists of a description of the morphology of the blood together with the methods of testing the various chemical and physical properties of blood. In Lecture II the origin and theories

of origin of the cellular constituents of the blood is first considered. The pathological picture of the changes that take place in the bone marrow and lymphatic tissue in diseases of the blood is also considered in this lecture. The latter part of Lecture II and all of Lecture III is a consideration of the various forms of anemia and leukemia, purpura, hemophilia, and allied diseases. These diseases are not treated in any systematic or exact method. Particular attention is paid to the pathogeneses and etiology of the disease under consideration; but aside from this there is simply a random discussion of the newer phases of the disease. Symptoms are occasionally noted. Treatment is only mentioned in connection with hemophilia and leukemia. The author say but little advance has been made in the treatment of the latter disease and that the Röntgen ray treatment produces only temporary improvement, lasting for a year or two at the most. Apparently he is unaware of the splendid results achieved in this country by the *x*-ray treatment. The book is completed by an appendix dealing with the preparation and method of employing a few of the more valuable stains for blood films. J. H. M., Jr.

A Laboratory Guide in Bacteriology for the Use of Students, Teachers, and Practitioners. By Paul G. Heineman Ph.D., Associate in Bacteriology, University of Chicago. Second Edition, Pp. 210; 36 illustrations. Chicago: University of Chicago Press.

The second edition of this excellent technical guide in bacteriology has been considerably enlarged by the addition of chapters on subjects pertaining to the recently separated specialty of public health. In the preface the author indicates a rearrangement of subject matter to permit of ready reference. Prof. E. O. Jordan supplies the introduction. The subjects covered comprise technique, general bacteriology, including an introduction to the various groups of bacteria, admirably arranged for a proper conception of the relations they bear to one another, and bacteriological examinations of water, sewage, milk, and soil, while the final section concerns the methods of study of yeasts and moulds.

The work presents a course as given by Heineman at the University of Chicago, and apparently includes the methods he believes feasible to teach to students. The methods for analysis in regard to public health are excellent, and while some are still *sub judice* with the profession, the student will obtain a clear understanding upon which to form a later judgment. A techinque for mycology is not often included in bacteriological books, and is welcome here. Incidentally, the instructions for students' behavior in the laboratory are excellent. This enlarged edition will be gladly received by those conducting similar courses. H. F.

PROGRESS

OF

MEDICAL SCIENCE

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UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

ASSOCIATE PROFESSOR OF MEDICINE, WASHINGTON UNIVERSITY, ST. LOUIS, MISSOURI.

The Phthalein Test. An Experimental and Clinical Study of Phenolsulphonephthalein in Relation to Renal Function in Health and Disease.—L. G. ROWNTREE and J. T. GERAGHTY (*Arch. Int. Med.*, 1912, ix, 284) describe their technique of injecting and measuring the excretion of phthalein, using 6 mgms. subcutaneously, intramuscularly, or intravenously, and recording the time of appearance of the drug, and the amount excreted in the urine in one and two hours. This is done by the Duboscq colorimeter, their modification of the Autenrieth-Konigsberger colorimeter, or by graduated cylinders. Excretion in health following different methods of administration has been studied in detail. Experimentally the time of appearance was shortest after intravenous injection and more rapid following intramuscular than subcutaneous. In humans Rowntree and Geraghty believe that absorption plays a small role when one hour determinations following intralumbar injections are employed. The average output is 57.5 per cent. Administration into the lumbar muscles is the method of choice. Experimentally, the influence of diuretics was studied. It was found that those drugs which stimulate the secreting cells, slightly increase the phthalein output, while those which act by changes in blood or osmotic pressure have no effect. In patients, no appreciable difference in output could be detected with the therapeutic dose of common diuretics. Since the kidney shows a specificity for phthalein, it was attempted to discover to which part of the kidney this action belonged. By using the renal system in frogs, it was shown that phthalein could be excreted by the tubules. Presumably this is true of mammals. In experimental acute tubular nephritis, there is marked diminution in output, while there is

little diminution in the early stages of the acute vascular nephritis. Hence Rowntree and Geraghty conclude that the glomeruli play a subsidiary part in the excretion of the drug. Five cases of acute nephritis were studied. There was a marked decrease in phthalein output when the clinical condition was grave. Twenty-five cases of chronic parenchymatous nephritis were studied. In mild cases very little disturbance of function was indicated. But where the drug is excreted in traces or not at all, a grave prognosis should be given though no signs of uremia exist. Twenty-three cases of chronic interstitial nephritis were studied. The test proved of immense value in revealing the degree of destruction of renal substance, and demonstrated itself to be of extreme importance for diagnosis and prognosis. Twenty-five cases of uremia were studied. In all, for two hours the phthalein elimination was zero or a faint trace. Thirty-three cases of broken compensation or in which cardiac insufficiency was associated with varying grades of true nephritis were studied. Rowntree and Geraghty found that decrease in function accompanies marked passive congestion without nephritis, but as the condition improves the phthalein output increases. Rowntree and Geraghty believe that in cases of obstruction of the lower urinary tract, a marked decrease in phthalein output invariably means severe derangement of renal function. The test, in conjunction with the clinical condition is of more value than the study of total urine, solids, nitrogen, and urea. Rowntree and Geraghty describe the technique of the phthalein test as applied to estimation of the function of the individual kidney by means of ureteral catheterization. In no instance was there inhibition of function as the result of this to seriously interfere with the value of the test. In unilateral disease in proportion to the decrease in function on the diseased side, approximately there was a proportionate increase in function on the healthy side. In bilateral disease it was possible to determine the individual function of each kidney and whether it was normal, less, or greater than normal. On the whole, Rowntree and Geraghty believe that phenolsulphonephthalein is better adapted for use as a functional test than any other drug previously employed for this purpose, on account of its early appearance in the urine, and the rapidity and completeness of its elimination by the kidney.

A Method of Reducing Excessive Frequency of the Heart Beat, by Means of Rhythmical Muscle Contractions Electrically Provoked.—W. HAMPSON (*Proc. Roy. Soc. Med.*, 1912, v, 119), reports that the stimulation of muscles by means of pulsating electrical currents causing alternate contraction and relaxation have a beneficial action on their development. The Bergioné system allows for the passage of current through large muscle areas without discomfort. Schott's method of treatment for suitable cardiac cases by properly graduated exercise has long been familiar. The application of these principles in heart disease produces results of interest and importance. Muscular contraction squeezes out blood from the veins towards the heart, the action of the valves securing its passage in the right direction. The subsequent relaxation allows the veins to fill and receive more blood than if they had not been so completely emptied. Thus the muscles become a modified heart. If the muscular contractions are made nearly synchronous with the heart beat by electrical stimulation, the artificial

waves of blood pressure in the venous system reinforce the heart action coincident with its own impulse. In this way that portion of the stimulation to the heart depending on venous pressure is intensified sufficiently to bring the beats from approximate to exact synchronism with the muscular contractions. By pursuing this line of action, the pulse rate may be markedly lowered. Hampson believes that this method is useful in numerous cases of weak, dilated, or irritable hearts. It increases the pressure on the right side of the heart, producing a better pulmonary circulation to relieve dyspnea; at the same time the heart is relieved of some of the muscular effort necessary to maintain the flow of blood, so that a greater amount of circulation work is done with the heart in a partially resting condition.

Bacteriology and Pathology of the Tonsils with Especial Reference to Chronic, Renal, and Cardiac Lesions.—David J. Davis (*Jour. Infect. Dis.*, 1912, x, 148) reports that the relation of tonsillar infection to lesions existing in other regions, especially in joints, heart, and kidneys, has received much attention from the clinical side. But bacteriological work in such cases is incomplete. Davis has studied 113 hypertrophied tonsils from cases of arthritis, nephritis, endocarditis, and tonsilitis without serious complications, taking smears and cultures from both the surface and crypts of the extirpated glands. Of 25 cases of arthritis, 25 showed hemolytic streptococci as the predominating growth. Seventeen of these strains were inoculated intravenously into rabbits, causing in 15 cases joint lesions and in 1 endocarditis. Of 10 cases of nephritis, 9 showed hemolytic streptococci predominating; 8 of the strains in rabbits caused lesions in joints or tendon sheaths. In all the kidneys and urine showed no abnormalities. Of 10 cases of endocarditis, 6 showed streptococci and 4 pneumococci predominating. Three of the latter group were injected in rabbits, producing in 2 cases vegetative endocarditis. Of 61 cases of tonsillar hypertrophy, 57 showed streptococci predominating. Seven of these strains produced rabbit arthritis as did one, from a case of multiple neuritis without arthritis or endocarditis. The therapeutic results of tonsillectomy furnish the best argument that infected tonsils bear a relationship to arthritic, renal, cardiac, and other clinical conditions. Davis believes that the occurrence in the tonsils of pure streptococci without any other significant germ would seem to point to these organisms as etiological. The reason why in one case nephritis is producedand in another arthritis probably lies in varying local susceptibility of the individual's tissues, rather than in any peculiar specificity of the infecting germs. Finally, Davis believes from his experimental evidence, that streptococci produce arthritis, only occasionally localizing on heart valves, while pneumococci produce arthritis rarely, but frequently localize on the endocardium. This observation was paralleled by the few clinical cases studied.

Abscess of the Lung and Liver. Simple Cure of a Chronic Case by the Upside-down Position.—W. M. McKechnie (*Lancet*, 1912, clxxxii, 865) cites the following case. A boy, aged fourteen years, had coughed up a teacupful of pus night and day for five years. Physical examination showed dulness at the right base continuous with liver dulness.

Over this area the breath sounds were nearly absent, while above moist rales were heard. On the affected side the diaphragm moved only slightly. McKechnie believed the patient had a liver abscess with perforation of the diaphragm and pleura; and was intermittently evacuating the cavities through the bronchi. McKechnie's treatment was as follows: The patient was placed over the edge of a table, head downwards, with the whole body hanging upside down. The legs and thighs on the table, lay at right angles to the trunk and thus supported it. In this position the patient coughed and squeezed until no more pus came out. The maneuver was repeated five or six times daily. In this way at first, the patient got rid of large quantities of pus which rapidly diminished and in six weeks stopped. The general condition improved markedly. McKechnie suggests that this method should be tried in abscess of the lung and bronchiectasis before resorting to the more formidable surgical procedures.

The Blood Picture in Disease of the Glands of Internal Secretion.—L. BORCHARDT (*Deutsch. Arch. f. klin. Med.*, 1912, cvi, 182) has extended the study of the blood in disease of the glands of internal secretion. Within the last few years diseases of the thyroid gland have been studied in particular. The present observations are of interest in connection with the findings in thyroid disease, because of the similarity of the blood pictures. Borchardt finds that not only in Basedow's disease, but also in all other diseases of the thyroid, hypophysis, and adrenals the blood is characterized in the majority of cases by a relative and absolute increase of the mononuclear cells, particularly the lymphocytes. In about half of the cases there is also a leukopenia and eosinophilia is about equally frequent. Similar changes are found in the blood of patients with the clinical signs of status thymolymphaticus. Since clinical and anatomical evidence of status thymo-lymphaticus is at hand in many instances of disease of the thyroid, hypophysis, and adrenals, it is possible that the blood picture in such cases is attributable to the status lymphaticus.

A Source of Error in Nylander's Test for Glucose.—E. STRAUSS (*Münch. med. Woch.*, 1912, lix, 85) found a negative Nylander's test for sugar in the urine of a diabetic, whose urine was shown to contain an abundance of sugar by the Fehling and polariscopic methods. It was found that the patient was receiving inunctions of iothion (d-iiod-oxypropan). On adding this substance to diabetic urine or to solutions of sugar, the Nylander reaction became negative, though there was no interference with the reduction of copper. The addition of potassium iodide or iodine is without effect. It appears that the iothion is excreted in the urine as such and forms some combination with the bismuth which prevents its reduction.

Diastase in Urine and Feces.—A. LINDEMANN (*Zeitschr. f. klin. Med.*, 1912, lxxv, 58) has studied the excretion of diastase in urine and feces, particularly in pancreatic disease. With normal gastric secretion the normal diastatic content of the urine is between 15 and 45 units (Wohlgemuth's method); that of the feces is about 200 units. In anacidity of the stomach the diastase of the urine and feces is

moderately increased. It is probable here that Wohlgemuth's suggestion that the salivary diastase, escaping destruction in the stomach, accounts for the increase, is correct. With hyperacidity normal values are again found. Continuous hypersecretion of the stomach, whether accompanied by hyperacidity or not, is usually associated with a similar hypersecretion of pancreatic juice. In this condition the urine may contain 50 to 800 units of diastase, with simultaneous increase of fecal diastase to 2000 units and more. This shows that examination of the urine alone may lead to error, since increase of diastase occurs with gastric hypersecretion as well as with diseases of the pancreas. There is, however, this important difference: While with pancreatic disease, the amylolytic enzyme of the feces is totally lacking or present only in traces, with gastric hypersecretion fecal amylase is very greatly increased. It is evident, therefore, in the application of this diagnostic procedure that determinations of diastase should be made on both urine and feces in doubtful cases.

A New Method for the Determination of Total Nitrogen in Urine.—O. FOLIN and C. J. FARMER (*Jour. Biol. Chem.*, 1912, xi, 493) describe a method for determination of total nitrogen in the urine, which, in principle, is a microchemical method based on the Kjeldahl-Gunning process for decomposing nitrogenous materials and on the methods of Nessler and of Folin for the determination of ammonia. *Method:* "Five c.c. of urine are measured into a 50 c.c. measuring flask if the specific gravity of the urine is over 1.018, or into a 25 c.c. flask if the specific gravity is less than 1.018. The flask is filled to the mark with water and inverted several times to secure thorough mixing. One c.c. of the diluted urine is then measured into a large test tube made of Jena glass (size 20 to 25 mm. by 200 mm.). To the urine in the test tube add 1 c.c. of concentrated sulphuric acid, 1 gram of potassium sulphate, 1 drop of 5 per cent. copper sulphate solution, and a small, clean quartz pebble (to prevent bumping). Boil over a micro-burner for about six minutes, *i. e.*, about two minutes after the mixture has become colorless. Allow to cool about three minutes, until the digestion mixture is beginning to become viscous (it must not be allowed to solidify). Then add about 6 c.c. of water, at first a few drops at a time, then more rapidly, so as to prevent the mixture from solidifying. To the acid solution is then added an excess of sodium hydrate (3 c.c. of saturated solution) and the ammonia is aspirated by means of a rapid air current into a measuring flask (volume 1000 c.c.) containing about 20 c.c. of water and 2 c.c. of $\frac{n}{10}$ hydrochloric acid. The air current used for driving off the ammonia may well be rather moderate for the first two minutes but thereafter for eight minutes should be as rapid as the apparatus can stand. Now disconnect, dilute the contents in the flask to about 60 c.c., and dilute similarly 1 mgm. of nitrogen in the form of ammonium sulphate, to about the same volume in a second measuring flask. Nesslerize both solutions as nearly as possible at the same time with 5 c.c. of Nessler's reagent diluted immediately before hand with about 25 c.c. of water. (Five c.c. of Nessler's reagent gives the maximum color with 1 to 2 mgms. of ammonia, and when diluted as indicated, turbidity is avoided.) The color produced does not react the maximum till the

end of about half an hour, but the increase is small and is immaterial to the result when the reagent is added as described, *i. e.*, practically simultaneously to the standard and to the unknown ammonium salt solution. The two flasks are therefore at once filled to the mark with distilled water, mixed, and the relative intensity of the colors is determined by means of a colorimeter . . . The reading of the standard divided by the reading of the unknown gives the nitrogen in milligrams in the volume of urine taken." For further details, the original should be consulted. The ammoniun sulphate used as the standard must be be specially prepared, as described by the authors.

The Radiologic Examination of the Apices of the Lungs. The "Cough Phenomenon."—S. KRENZFUCHS (*Münch. med. Woch.*, 1912, lix, 80) refers to the well-known facts that apices of individuals with long thorax and wide intercostal spaces are clear in health, whereas with a short thorax and narrow interspaces there is usually a shadow over the apices on radiologic examination. In the latter instance it is claimed by some that the shadows disappear during deep respiration, though Krenzfuchs finds such a result exceptional. He has noted, however, that normal apices, which cast shadows—whether from atelectasis or from the conformation of the thorax—become clear when the patient coughs. This clearing of the apices during cough he designates the "cough phenomenon." (Hustenphänomen). The explanation of the phenomenon is as follows: The deep inspiration preceding the cough fills the lower parts of the lungs. With the cough, the contracture of the abdominal muscles and the passive elevation of the diaphragm force the air into the apices of the lungs, since the glottis is closed. Inflation of the apices is the result. The examination is made with a soft tube and weak current. During cough, the head is turned away from the apex examined, when the antero-posterior position is used. The value of the "cough phenomenon" is chiefly in the differentiation between atelectatic and infiltrated apices. The former become clear during cough, while the latter remain dark or clear only partially.

On the Determination of Ammonia in Urine.—O. FOLIN and A. B. MACALLUM (*Jour. Biol. Chem.*, 1912, xi, 523) have devised a new method for the quantitative estimation of ammonia in the urine. "Into a test tube measure by means of Ostwald pipettes 1 to 5 c.c. of urine. (The volume taken should give 0.75 to 1.5 mgms. ammonia-nitrogen. With normal urine 2 c.c. will most often give the desired amount. With very dilute urines 5 c.c. may be required, while with diabetic urines rich in ammonium salts even 1 c.c. may give too much, and the urine must be diluted). Add to the urine a few drops of a solution containing 10 per cent. of potassium carbonate and 15 per cent. of potassium oxalate, and a few drops of kerosene or heavy, crude machine oil (to prevent foaming). Pass the strong air current through the mixture for ten minutes (or as long as is necessary to drive off all the ammonia) and collect the ammonia in a 100 c.c. measuring flask containing about 20 c.c. of water and 2 c.c. of $\frac{n}{10}$ acid. Nesslerize as described under total nitrogen and compare with 1 mgm. of nitrogen obtained from a standard ammonium sulphate solution and similarly Nesslerized."

SURGERY

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D.,

FORMERLY JOHN RHEA BARTON PROFESSOR OF SURGERY IN THE UNIVERSITY OF PENNSYLVANIA AND SURGEON TO THE UNIVERSITY HOSPITAL,

AND

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL, AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Further Experiences with the Treatment of Volkmann's Ischemic Paralysis and Contraction by the Method of Robert Jones.—SAYRE (*Amer. Jour. Orthop. Surg.*, 1912, ix, 557) summarizes his conclusions as follows: Volkmann's ischemic paralysis is the result of a myositis set up by obstruction to the supply of oxygen by pressure either by bandages, splints, or sometimes by position and pressure of the bone fragments. Shortening of the affected muscles results, the muscles of the forearm being those usually affected, those of the hand occasionally. Massage is too intermittent to produce good results. Shortening of the bones and removal of scars pressing on nerves have given good results. Jones' method of constant traction on contracted muscles produces results when massage fails, as it is a constant instead of an intermittent force. In some cases bone growth at a faster rate than muscle growth may cause recurrence of the deformity in a way analogous to the recurrence of equinus in cases of paralysis of the leg, and a second stretching may then be necessary.

Pyelotomy in Renal Calculi.—BAZY (*Jour. d'Urol.*, 1912, i, 739) adds 3 interesting cases to those which he has previously reported. The calculi were large and ramifying, the only kind which, in Bazy's opinion, deserve publication, the small calculi being of only secondary interest. He insists that the radiograph will locate the calculus and determine in advance if a pyelotomy or nephrotomy is indicated. Every calculus, the internal border of which, according to the radiograph, is less than 5 cm. from the median line, is in the renal pelvis. Those situated more externally, are in the kidney substance. The shadow of the calculus should be at the level of the third lumbar spine or the junction of the second and third. The shock of pyelotomy is reduced to a minimum and the hemorrhage is slight. It is the incision into the kidney substance which bleeds freely, and in some cases the hemorrhage has been so abundant as to call for a nephrectomy. More frequently than some authors believe, a fatal secondary hemorrhage has taken place. Even if renal calculi cannot always be removed by a pyelotomy, they can be removed by this means more often than is thought, and Bazy can remove some by this method which are in the renal parenchyma. Pyelotomy permits lavage of the pelvis for infection,

which a nephrotomy does not, since the pelvis is being compressed with the vessels for hemostasis. Bazy calls pyelotomy the operation of choice for the removal of renal calculi, nephrotomy the operation of necessity.

The Mode of Origin of Renal Tuberculosis.—RAFIN (*Jour. d'Urol.*, 1912, i, 779) studied 160 cases upon which he did a nephrectomy for renal tuberculosis, to determine the clinical or apparent beginning of the disease. In 99 of the cases, or 61.87 per cent., the first symptoms were vesical, and these he therefore called the signal-symptoms. Renal pain, vague heaviness, torture, or more rarely painful crises simulating renal colic; less often mark the beginning of the affection. They are important, however, because while more fugacious than the vesical symptoms, less troublesome, and less characteristic, they annoy the patient so little that he ascribes them to some rheumatic affection, or to a cold, a movable kidney, etc., and in consequency neglects or forgets them. For this reason they may be the first symptoms of the disease more frequently than the patients state. In a small number of cases, hematuria will be the first symptom noted. Exceptionally, an analysis of the urine reveals the presence of albumin as the first sign of the disease, or the patient perceives that the urine is turbid. It is exceptional for the patient first to observe a disturbance of his general condition. It is often striking to observe the contrast between the grave renal lesions and the preservation of a good general condition.

A New Operation to Reëstablish the Continuity of the Intestine after an Extensive Resection of the Sigmoid and Rectum.—VIGNOLI (*Archiv. gén. d. chir.*, 1912, vi, 621) proposes a method of reëstablishing the continuity of the bowel after a considerable portion of the rectum and sigmoid have been removed, by grafting between the two remaining cut ends of the large bowel, a corresponding portion of the lower ileum. He first carried out experiments on dogs to demonstrate its feasibility and to perfect its technique. Later he performed the operation on the cadaver to adapt it to the different anatomical conditions in the human. Still later came the opportunity to practise the operation on a live patient. In describing the technique, he emphasizes first the necessity of choosing a portion of the ileum which from the position of its mesentery, will permit it to best fit into the position it is intended to occupy. The mesentery attains its maximum length at about 40 cm. from the end of the ileum, nearly in the line of the superior mesenteric artery. The portion to be excised extends from this point upward and to the left. After dividing the ileum at the desired levels and the mesentery in radiating lines from the same points, at the lower end the mesentery is incised in the line of the intestine for 2 or 3 cm. and about 4 cm. from the intestine, in order that the excised portion of intestine can be straightened out. The continuity of the small intestine is then reëstablished by a circular enterorrhaphy and the cut edges of the mesentery brought together by a few sutures. The colonic end of the large bowel excised with the growth and the rectal end are fixed in their respective positions to the posterior abdominal wall by sutures. The portion of ileum transplanted into the gap is anastomosed at the colonic end of the divided

large bowel by a circular enterorrhaphy. A lateral anastomosis may be made, so that the open end of the colon may be employed for an artificial anus. At the rectal end after a preliminary preparation of the rectum, the lower end of the piece of small intestine is invaginated into it and fixed there by sutures. In the case operated on it was necessary to make a preliminary cecostomy, in order to allow free escape of the feces and relieve the toxemia, and to permit rest of the diseased portion of the bowel as well as local treatment. The ablation of the stenosed portion of the rectum and sigmoid was performed at another time, and the enteroplastic operation at a still later period. The patient did well after the operation, but died of metastatic recurrence of the disease after leaving the hospital.

The Operative Treatment of the Edema of Elephantiasis.—KONDOLEON (*Zentralbl. f. Chir.*, 1912, xxxix, 1022) refers to the work of Mikulicz, Lanz, and Handley for the removal of persistent edema. Lanz tried to establish a new collateral circulation in the thigh by strips of fascia passed into holes made in the femur and cutting multiple small holes in the fascia lata. Handley proceeding from the view that the sclerotic edema in the upper extremity in the later stages of mammary carcinoma was due to the obliteration of the lymph paths, attempted to make new paths for the obstructed lymph by means of silk threads from the hand to the loose subcutaneous tissue of the thorax. In a case of sclerotic edema from a crushing wound, Kondoleon modified the Lanz procedure by laying the fascial strips between muscles and leaving the ends of the fascial incision open. This method of making a communication between the subcutaneous tissue and muscles was carried out further in cases of elephantiasis. He found conditions during his operations for this condition which convinced him that neither the Lanz nor the Handley methods could be of service in elephantiasis. In every old case and independent of the cause of the hard edema, he found besides the known changes in the skin and subcutaneous tissues, the fascia always much thickened (up to 3 cm.), thickly infiltrated, adherent to the surrounding tissues, especially to the fatty tissue lying between the skin and fascia. The upper surface of the aponeurosis was irregular, and of milky appearance. Its under surface lying on the muscle had its normal smooth color and consistency. In some cases he could separate the fascia from the connective-tissue layer between the subcutaneous fatty tissue and the fascia. In other cases this layer could not be separated from the aponeurosis. The greater quantity of the retained lymph came from the region of this thickened aponeurosis. The underlying muscles were found microscopically and macroscopically to be normal. These findings led to the conclusion to make a wider communication between the subcutaneous tissue and muscles and to the development of the following technique: When only the leg was involved, he made two incisions the whole length of the limb, one on the outer and one on the inner side of the leg. When the whole limb was involved, he made four incisions, two in the thigh and two in the leg. The skin is separated and retracted by broad hook retractors. The infiltrated fatty tissue covering the fascia is excised, and the fascia is thus exposed, when a piece of it is removed, the length of the

incision and the width of three to four fingers. The muscles bulge forward. Complete hemostasis is provided and skin sutures introduced without drainage. This operation was performed on 6 cases. In 2 the operation was repeated and in 1 of thirty years' duration, it was done the third time. The technique was changed each time until the above described technique was employed in the third operation, by which a good result was obtained. Not enough time has elapsed to permit definite results, but they are already satisfactory and prove the value of the method.

Supraclavicular Anesthetization of the Brachial Plexus.—Borchers (*Zentralbl. f. Chir.*, 1912, xxxix, 873) says that Schleich's infiltration method of local anesthesia is gradually being displaced by Braun's method of anesthesia produced by injecting the large nerve trunks with a local anesthetic fluid, and that not only may we do small operations on ambulatory patients by local anesthesia, but major operations as well. By combining the method with the use of scopolamin, pantopton, morphine, or other drugs, we may do severe operations on very nervous and excitable people. When necessary we can now do such operations on any part of the body. Borcher began to employ the method of injecting the brachial plexus soon after Kulenkampff's first paper on this subject, and is now prepared to report on the results in 35 cases. (For abstract on Kulenkampff's paper, including the technique of the method see the January number of this Journal, p. 134.) Borcher says that Kulenkampff showed before the 1912 surgical congress, and he himself has found, that a puncture of the arterial wall is without importance. According to his experience, the anesthesia comes on in from three to thirty minutes, depending upon the strength of the solution and the distance from the nerve at which the injected fluid is deposited. It occurs more quickly when the nerve itself is injected than when the needle goes through the nerve. The duration of the anesthesia with paresis or paralysis of the muscles is about one and one-half to two hours. Borcher thinks that the degree of paralysis of the muscles will be proportionate to that of the anesthesia. The latter was sufficiently marked to render the most severe operations on the upper extremity painless. Usually the whole arm up to the shoulder girdle is without pain. Occasionally there was some feeling in a narrow strip along the postero-internal side of the arm from the axilla to the elbow, corresponding to the supply of the cutaneous branch of the median nerve. It was observed also that notwitnstanding that the operation on the forearm was painless, the application of the Esmarch bandage to the arm was unpleasant. In one case there was observed a palsy of the radial, median, and ulnar nerves, which lasted several weeks and gradually disappeared.

Anesthesia of the Sciatic Nerve.—Jassanetzky-Woino (*Zentralbl. f. Chir.*, 1912, xxxix, 1021) has been working for three years to perfect a technique for the injection of the sciatic nerve with an anesthetic fluid, and he has finally found the point where the nerve can be easily and safely attacked. It corresponds to the junction of a horizontal line passing through the top of the great trochanter and a vertical

line through the margin of the tuberosity of the ischium. In 3 out of 20 cadavers, the horizontal line was from 1 to 1.5 cm. too high. In all the others the junction of these two lines was exactly at the point where the nerve, immediately after making its exit from the great sciatic foramen, lies directly on the bone. Almost without exception, colored gelatin injected at this point was found by dissection either directly over or under the nerve or within the nerve substance. In most of his clinical cases, the injection of the sciatic and anterior crural nerves was combined, and in all operations during the work on the soft tissues the anesthesia was complete. During the manipulations of the bone, as in lifting the periosteum or sawing the bone, considerable sensibility remained. In the more recent cases, he has injected, not 10 but 15 to 20 cm. of the novokain solution with 7 to 10 drops of adrenalin, and in this way he obtained an anesthesia complete enough to permit him in a man, aged seventy-eight years, to amputate the anterior portion of the foot for gangrene. The technique of the injection is as follows: The patient is placed in the prone position and the point for the injection is determined as above stated. An 8 cm. long needle is introduced at right angles to the surface down to the bone. When the bone is not struck, the needle is tried somewhat higher or further outward from this point. When the needle strikes the bone it is withdrawn a few millimeters and 10 c.c. of a 2 per cent. novokain-adrenalin solution is injected for operations on the soft tissues, 15 to 20 c.c. for operations on the bone. In the former cases, the operation may be begun after a half hour, in the latter not sooner than an hour after the injection. This method was employed in 12 cases. In only 1 did no anesthesia develop. In all the others, however, the soft tissues were anesthetized completely and the bones in varying degrees. In most cases it will be necessary to inject the anterior crural nerve also as Läwer advised. The skin supplied by the obturator nerve is so small in area that it can be injected with a small quantity of the fluid.

Investigations Concerning Surgical Methods of Treatment for Trigeminal Neuralgia.—Otto (*Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1912, xxv, 78) considers that the justification of the operative treatment for trigeminal neuralgia is generally recognized, but that just which operation should be done in a given case is not an easy question to decide. Neither the peripheral operations nor the resections at the base of the skull, will always give permanent relief. Even the extirpation of the ganglion in many cases gives only temporary relief, probably because of incomplete operations. Only rarely do we find the seat of changes in the nerve and the mode of origin of the neuralgia is rarely determined. Nor do we know whether the neuralgia is due to functional or organic disease. As the result of his studies, Otto believes that the peripheral operations are frequently followed by recurrence. Thiersch's nerve exeresis in most cases leads to recurrence, very frequently after a few months. The condition recurs more rarely after resections at the base of the skull. Extirpation of the Gasserian ganglion gives the best results, provided the ganglion is wholly removed. The operation is, however, technically difficult and should be reserved for otherwise hopeless cases and especially for those in which the three

branches of the ganglion are involved. Under these circumstances, one is fully justified in trying out the injection method of combating the affection. Alcohol (70 to 80 per cent.) is the most suitable fluid with which to inhibit the conductivity of the nerves without damaging the other tissues. The deep injection at the base of the skull suffices even in severe cases to anesthetize the regions supplied by the treated branches for months, and it can be repeated without danger. The effect usually lasts a long time, but whether a permanent cure may result remains to be proved. The Offerhaus method is favored because it is easily performed without previous practice. It is without danger, and may be employed to obtain anesthesia for the performance of operations in the trigeminus regions.

End Results of Fracture of the Shaft of the Femur.—Estes (*Annals of Surgery*, 1912, lvi, 162) summarizes the conclusions on 760 tabulated cases of fracture of the shaft of the femur as follows: The records of fractures are kept very incompletely and it is quite impossible in the United States to obtain anything like full, accurate, and reliable data of a large number of finished cases. The largest number of cases of fracture of the shaft of the femur occurs in men aged between twenty and fifty years. Children aged under ten years have the next largest number. Working people furnish the largest number of cases, though data in regard to this point are not kept in the majority of cases. Indirect violence produces by far the largest number of these fractures. Of the reported cases, the middle third of the bone is most frequently broken, the lower and upper thirds are almost equally involved. Simple fractures far outnumber the compound and complicated ones. The average shortening before reduction is 1.38 inch. By far the most frequent method of treatment was by some form of Buck's extension. An anesthetic was not used to assist reducing the fractures in the majority of reported cases. The average weight used in extension was 14 pounds. (This is too little weight.) The average reported shortening of completed cases is one-half an inch. Average length of time in bed, 8.2 weeks. Average length of time incapacitated, 2.7 months. (This is probably a mistake.) Average length of time crutches, canes, or other aids in walking were used, 8 weeks. Limp was present for some time in the large majority of cases. A little more than one-tenth of the cases had excessive callus which produced some disturbance. Nearly all the reported measurements were taken from the anterior superior spine of the ileum to the internal malleolus. Disability estimated by: (*a*) Endurance, (*b*) pain, (*c*) swelling, (*d*) interference with joint function; present in about 1 case in 25. Death rate of reported cases, 3.69 per cent. (This Estes believes is a mistake.) Chief causes of death: (*a*) Pneumonia, (*b*) shock and exhaustion, (*c*) delirium tremens. Estes' first recommendation and deduction from his work is that teachers in medical schools should give far more attention than they have done in the last decade or more to their own investigations of fractures, and to the teaching of this most important branch of surgery to the students who belong to their classes. Second, while recognizing the fact that *x*-ray photographs may be most misleading, the writer believes, nevertheless, when taken by competent anatomists who understand the importance of proper

relative position of tube and limb, and the importance of taking more than one view of the fracture, these radiographs will furnish an indication for the proper reduction and the mechanical appliances for the preservation of proper apposition, and they will serve as a graphic record of the fracture itself. Estes finds that in most cases treatment by some form of traction enables the patient to resume his occupation and function without serious detriment. In selected cases, where it is impracticable to restore the fragments to their proper position, and where mechanical means have failed within a reasonable time to produce proper restitution of the fragments, the open method may be employed, but then only by an experienced surgeon, one who habitually employs most thorough aseptic methods. The results may be considered good if the measurements show no more than an inch of shortening, provided there is no inversion or eversion of the foot from angulation of the fragments.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF APPLIED THERAPEUTICS IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

The Treatment of Diphtheria Infection by Means of Diphtheria Endotoxin.—HEWLETT and NANKWELL (*Lancet*, 1912, clxxxiii, 143) tested the effect of diphtheria endotoxin on diphtheria patients of whom many had harbored the diphtheria bacilli for many weeks or months after the acute attack. After one or more injections of the endotoxin all the patients showed definite improvement. In many the diphtheria infection ceased entirely; in some it persisted, and the patient remained uncured; but even in these unsuccessful cases they noted invariably a diminution in the number of bacilli. The endotoxin is prepared by growing a virulent culture of diphtheria bacillus on serum or blood agar, collecting the growth, washing it two or three times in sterile physiological salt solution so as to remove the toxin, grinding the bacterial mass in the presence of intense cold, and filtration of the ground mass through a Berkefeld filter. The filtrate contains the endotoxin and is standardized by the addition of sterile salt solution so as to contain from 2 mg. to 5 mg. per cubic centimeter. With regard to dosage, they first used the endotoxin in doses of from 0.5 mg. to 1.0 mg., but the patients did not do so well as when they gave an initial dose of 2 mg. At the end of a week or ten days, if the culture was still positive, a second injection of 5 mg. was given and this, if necessary, was repeated later. The dose was the same for children and adults. No ill effects, except some redness and tenderness around the site of injection, followed the administration of the endo-

toxin. Only one patient showed any general disturbance, and that merely by a transitory rise of temperature and a feeling of malaise. Hewlett and Nankwell give details of 24 cases treated by this method. They advise the use of endotoxin as an aid to the antitoxin treatment, and consider that its greatest value lies in the reduction of the number of possible diphtheria carriers.

Collapse Produced by Hormonal.—ZUELZER (*Deutsch. med. Woch.*, 1912, xxxviii, 1233) advances an explanation for the symptoms of collapse reported by many different observers as occurring after the intravenous administration of hormonal. Zuelzer says that hormonal had been given over a period of two years by the intravenous method over 4000 times without any untoward effects. Then, suddenly, reports of marked collapse after the administration of hormonal began to appear in the literature, including one fatal case. Zuelzer was inclined at first to attribute these untoward results to technical faults in the administration. His practise always has been to allow the hormonal to enter the vein very slowly, drop by drop. However, with all technical precautions on his part, he had 4 cases of collapse in quick succession in his own practice. A laboratory investigation of the hormonal on hand showed the presence of an albumose. Zuelzer attributes the toxic action to the substance that appeared to be formed during the process of manufacture. The hormonal now manufactured is free from this albumose, according to Zuelzer. He gives the pulse and blood pressure readings in a few cases after the administration of the new hormonal intravenously that show they were little influenced by the injections.

Report of a Case of Diabetes Insipidus with Marked Reduction in the Amount of Urine following Lumbar Puncture.—HERRICK (*Arch. Int. Med.*, 1912, x, 1) reports a case of diabetes insipidus in which there were symptoms pointing to a cerebral origin of the disease. A man, aged forty-three years, had for four years the typical manifestations of diabetes insipidus. The urine varied in amount from 7500 to 11,000 c.c., and was always of low specific gravity, 1001. Lumbar puncture was made for the purpose of investigating the cause of the trouble. Less than 5 c.c. were withdrawn, the fluid escaping slowly under low pressure. Within forty-eight hours the daily amount of urine had dropped to 660 c.c. Headache, pain in the back of the neck, anorexia and vomiting, with a feeling of general weakness followed the puncture. Morphine was given for pain and almost no fluid or food was taken for three or four days. But after the prostration following the lumbar puncture had disappeared and when food and water were freely taken, there was no thirst, as before, and the amount of urine for a period of four weeks never exceeded 1800 c.c. for twenty-four hours. The specific gravity averaged 1015, ranging from 1005 to 1031 (single specimen). The result of the puncture suggests that the cause of the polyuria in this case was a lesion of the brain, perhaps in the hypothesis. This case also seems to indicate that, under certain conditions, the kidney of diabetes insipidus can, at least temporarily, pass a concentrated urine. Herrick gives a detailed history of the case in his article.

Splenic Anemia Treated with Salvarsan.—PERUSSIA (*Münch. med. Woch.*, 1912, lix, 1482) reports the case of a woman, aged thirty years, with very marked anemia, marked enlargement of both liver and spleen, edema, and suffering from persistent vomiting and diarrhea. The clinical picture was that of splenic anemia. The patient received three intravenous injections of 0.3 grams of salvarsan during a period of four weeks, and at the end of this time was apparently cured. Perussia does not know whether to attribute the good affects of the salvarsan to arsenic or to a possible spyhilitic basis for the trouble, or to a specific action of the salvarsan against the unknown cause of splenic anemia. VALLARDI (*Münch. med. Woch.*, 1912, lix, 1483) reports the case of a young man, aged twenty-two years, with very marked anemia and enlarged spleen. In this patient there was the history of a malarial attack lasting three months about one and one-half years before coming under Vallardi's observation. Operation was contraindicated by the enormous size of the spleen and a tendency to hemorrhage, and also by the poor general condition of the patient. He was given three intravenous injections of salvarsan (0.15, 0.4, and 0.4 gram), and an apparent cure resulted.

A Preliminary Report on Neosalvarsan, with Particular Reference to its Employment as an Intramuscular Injection.—WOLBARST (*Medical Record*, 1912, lxxxii, 145) gives the results of his clinical experience with Ehrlich's neosalvarsan. He believes that its effects are at least as striking as those of salvarsan. The reaction after treatment is slight with correct technique. Larger doses are better tolerated than is the case with salvarsan. The neutral reaction of the solution in water obviates the use of sodium hydrate, thus avoiding the possibility of thrombosis. Leakage of neosalvarsan solution into the tissues seems to be absorbed much more quickly than salvarsan. Neosalvarsan has no apparent effect on the eyes, kidneys, heart, or lungs. Intravenous injections of neosalvarsan may be repeated in two or four days. The neutral reaction of neosalvarsan solution lends itself readliy to intramuscular injection. Wolbarst advises for intramuscular injection a suspension of neosalvarsan in glycerin. Neosalvarsan powder is mixed in a mortar with 3 to 4 c.c. of glycerin; to this is added a few drops of a 1 per cent. beta-eucain or alypin solution in distilled water. The suspension has now been converted into an almost clear solution. The buttocks are painted with iodin and four spots are located into which 1 c.c. of the solution is injected. Most patients have felt practically no pain; some have felt pain on sitting or standing for a day or two. The induration caused by the injection is very slight.

The Influence of Theophyllin on Nitrogenous Excretion.—FARR and WELKER (*Arch. Int. Med.*, 1912, x, 23) studied the changes produced by theophyllin on the urinary nitrogen in healthy persons and in nephritics. Most clinicians consider that theophyllin is contraindicated in acute nephritis, and of doubtful utility in chronic nephritis. It is generally agreed that theophyllin meets its best indications in the passive congestion and edema of heart disease, especially when combined with digitalis. Farr and Welker found that theophyllin

promoted the excretion of fluid in 2 cases but apparently did not affect, or even slightly diminish the excretion of nitrogen. In a case of diffuse nephritis diuresis failed to develop and the nitrogen elimination was sharply reduced. In a case of chronic interstitial nephritis the urinary partition was apparently changed by the drug so that it approached more nearly the normal. This may have been due to natural causes incident to convalescence. The slight or doubtful influence of theophyllin on nitrogen excretion and its pronounced influence on the excretion of water and sodium chloride suggests to Farr and Welker that this substance may act principally on the capsule of Bowman and little if at all on the tubules. Its failure to act in a given case might then be attributed to extensive involvement of the glomeruli.

The Treatment of Syphilitic Diseases of the Nervous System by Salvarsan.—Collins and Armour (*Jour. Amer. Med. Assoc.*, 1912, lviii, 1918) record the results of eighteen months' experience, during which time 75 patients suffering from syphilitic nervous disease were treated with salvarsan. They believe that the salvarsan treatment is effective but that in order to exert its best results, large doses must be given and frequently repeated. Of 36 cases of tabes in various stages of the disease, 22 showed striking, and in some instances, remarkable improvement both subjective and objective. In nearly every instance there was a decided increase of weight and a subjective feeling of improvement. The pain was lessened or relieved in many instances, and in the majority of cases, the ataxia was very much improved. In 2 cases, the pupils regained their capacity to react to light. Many of these patients had been under observation and treatment for many years, and the results obtained by salvarsan therapy were incomparably better than those obtained by mercury. They did not supplement the salvarsan treatment in these cases by the use of mercury, and did not give iodide of potassium, for they have long believed that iodide of potassium is injurious rather than beneficial in the treatment of tabes. Salvarsan was given systematically in 9 cases diagnosticated as general paresis. In 2 of these it was difficult to say whether the diagnosis should be tabes or paresis. It was in these 2 cases and in 1 undoubted case of paresis that great improvement took place. The improvement in the undoubted case of paresis seemed to be much more marked than the spontaneous remissions often occurring in the course of paresis. The most gratifying response to treatment was observed in the cases diagnosticated meningitis and meningomyelitis. In only 2 out of 6 cases of cerebral endarteritis of luetic origin was any perceptibile improvement observed. Collins and Armour give details of a number of cases to illustrate the marked benefits derived from the salvarsan treatment of diseases of the nervous system of either direct or remote syphilitic origin. They are convinced that salvarsan is far more effectual than mercury for such cases.

Five Years' Experience with the High Calory Diet in Typhoid Fever.—Coleman (*Jour. Amer. Med. Assoc.*, 1912, lix, 363) has advocated that typhoid fever patients be fed on a more liberal diet on the ground that the requirements of the patient during the

febrile period are very inadequately met by a milk diet that has a caloric value of from 1000 to 2000 units. Coleman thinks that they require from 3000 to 5000 units. The number of foods originally employed was limited. With added experience the number has been increased until now the diet furnishes considerable variety. Coleman gives a table of appropriate foods with their approximate caloric values in his article. He believes that the foods most likely to prove harmful are meat and its preparations (except small quantities of meat broth, given for the purpose of stimulating the appetite and for sake of variety), vegetable foods containing much cellulose, and fruits containing much cellulose and small seeds, such as berries. Coleman answers some objections brought against the diet. It is claimed that patients cannot digest and absorb the amount of food recommended. He does not believe that typhoid fever causes severe impairment of the digestive powers. While there can be no doubt that food may cause disorders of digestion in typhoid, their occurrence depends not so much on the quantity as on the method of giving it. Sudden alterations in the diet, especially from a sparse to a rich diet, are likely to cause digestive disorders. Coleman believes that the majority of patients may be given the larger amounts of food not only without causing disturbances of digestion, but with the disappearance of previous indigestion. In regard to the capacity of the patient to absorb the larger amounts, investigations showed that the absorption of carbohydrate was practically complete, less that 0.5 per cent. being lost. The average loss of protein was 7.1 per cent. The average loss of fat in the active period of the disease, when the patients were taking from 147 to 200 grams, was 7.2 per cent.; in the steep-curve period and in convalescence, when the patients were taking from 150 to 258 grams, it was 4.5 per cent. The normal loss for similar diets is 3 per cent., but, according to Rubner, the loss of fat may react 7.1 per cent. in health. The objection that the amount of fat recommended would inevitably cause alimentary disorders and acidosis has likewise been proved to be without foundation. Coleman answers the objection that, granting its absorption, patients do not require the amount of food which is advocated, by stating that patients lose both nitrogen and weight if they do not receive it. As measured experimentally, the high calory diet furnishes from 1000 to 2000 more calories than are expended by the patient in twenty-four hours, but the clinical evidence is convincing, according to Coleman, that they require the excess. In comparing the results obtained by the high calory diet with those obtained under the ordinary diets, the mortality percentage was 8.7 per cent. in the high calory cases, as compared with 16 per cent. in the other group. Convalescence seemd to be distinctly shortened and the symptoms of toxemia disappeared as a result of giving sufficient food.

New Points of View in the Treatment of Diphtheria, Scarlet Fever, and Suppurative Processes.—Lorey (*Med. Klinik*, 1912, viii, 1069) says that the therapeutic action of antitoxin in the treatment of diphtheria that has prevailed at Hamburg in epidemic form during the last three years has been disappointing. He advances the question whether it might not be feasible to secure an antitoxin derived from a

local strain of diphtheria bacilli. He suggests that a strain of bacilli might be found that has a more marked action in inducing paralysis, and an antitoxin derived from this strain might be more effectual for the severer forms of diphtheria. Lorey has had good results with the local application of antitoxin to the eye, nose, or throat in diphtheria or scarlet fever. The antitoxin is diluted with physiological salt solution and applied locally on compresses when possible, or used in the form of a spray or gargle. The membranes break up and are thrown off, while there is a profuse watery secretion underneath. This action is not due to the antitoxin content, and similar effects are noted when fresh horse serum is used. The same local treatment has been equally effectual in the sore throat of scarlet fever and in various suppurative processes.

The Use of Hexamethylenamin in the Affections of the Upper Respiratory Tract.—Esenberg (*Jour. Amer. Med. Assoc.*, 1912, lviii, 2032) has used this drug in 43 cases, of which 22 were cases of acute bronchitis, 12 of acute rhinitis, 8 of influenza, and 1 of chronic sinusitis. It was given as follows: Children aged ten years received 4 gr. (0.3 gram) dissolved in one-half glass of water, three times a day during the first day, and twice a day during the following day or two. Children aged fifteen years received 6 gr. (0.4 gram) dissolved in a full glass of water, while adults received 10 gr. (0.7 gram) given in the same way. Cases of rhinitis were cured in from three to four days. In acute bronchitis every patient was well in four or five days, while influenza patients recovered in from five to seven days. No untoward symptoms were observed even when given in fairly large doses. This treatment seemed to prevent complications of acute rhinitis, such as bronchitis and sinusitis.

The Rapid Cure of Amebic Dysentery and Hepatitis by Hypodermic Injections of Soluble Salts of Emetine.—Rogers (*British Med. Jour.*, June 22, 1912, p. 1424) says that the principal objection to the ipecac treatment of amebic dysentery is the production of very disagreeable and exhausting nausea and vomiting by the large doses that are essential to obtain its curative effects. This drawback is only imperfectly overcome by giving the drug in salol or keratin coated capsules, and the use of opium, chloral hydrate, or tannic acid to check vomiting. Vedder has shown that emetine, the principal alkaloid of ipecac, has the power in high dilutions of destroying amebæ in broth cultures, although it is not clear that this was a pathogenic form, which most recent authorities believe has not yet been cultivated. Rogers has, therefore, tested the effects of the soluble emetine hydrochloride on ameba histolytica in dysenteric stools. He found that, on placing a piece of mucus containing numerous active amebæ in normal saline solutions of this salt, the pathogenic organism is immediately killed and materially altered in its microscopical appearances by a 1 in 10,000 solution, while after a few minutes they are rendered inactive, and apparently killed by as weak a solution as 1 in 100,000. He therefore decided to try if this powerful alkaline can be safely administered hypodermically in the treatment of amebic disease, and obtained striking results in a few patients.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Fatal Cases following the Early Getting up in Parturient and Operative Cases.—AICHEL (*Zentralblatt f. Gynäkologie*, 1911, No. 6) reviews Frommé's case of embolism in a primipara, aged nineteen years, who got up on the second day for one hour in the puerperal period. Autopsy showed complete closure of the pulmonary vessels from an embolus the thickness of a finger, and thrombosis of the pelvic veins. In the thrombi were found streptococci. Scherer's case was that of a patient who aborted at three months, and was curetted to remove the remains of the placenta. On the third day the patient sat up for half an hour. On the fourth day fever developed, with continued high temperature, until the patient's death on the sixtieth day. From the second week the patient had daily chills. On the seventeenth day there was pain in the left lower extremity; on the twenty-sixth day the femoral vein became tender; on the thirty-second day the patient had cough; on the forty-second day bloody sputum; and on the forty-fourth day left-sided pneumonia. The patient died suddenly on the sixtieth day. At autopsy, there was thrombosis of the veins of the pelvis, the hypogastric veins, the left common iliac, vena cava, and femoral; purulent parametritis, and pelvic peritonitis. There were metastatic abscesses in the lungs, and pleurisy. In analyzing these findings, Aichel comes to the conclusion that they give no positive evidence that the getting up of the patient was the cause of the fatal issue. Infection and thrombosis develop in patients who remain in bed the usual time.

The Technique of Suprasymphyseal Cesarean Section.—FRANK (*Zentralblatt f. Gynäkologie*, 1911, No. 6) has changed somewhat his method in suprasymphyseal section, and in his last 5 cases, where the cervix was completely dilated at the time of operation, he has closed the uterus and abdominal wound, and allowed the placenta to be delivered through the cervix and vagina. He believes this to be a distinct improvement in the performance of the operation. His reason for adopting this change lay in the fact that in cases where he had expressed the placenta through the wound there had often been severe hemorrhage.

The Development of Placenta Prævia.—JOLLY (*Archiv f. Gynäkologie*, 1911, Band xciii, Heft 1) contributes a paper based upon cases examined in Bumm's clinic in Berlin, where in three different patients the opportunity was afforded to study the development of placenta prævia. He finds that placenta prævia develops only when the ovum has its preliminary attachment in the lower portion of the

uterine cavity. The insertion of the ovum and its development seems to depend largely upon the place of impregnation. There was a distinct interval between impregnation and the permanent attachment of the ripe ovum. The nearer to the uterus in the tube impregnation occurs, the greater is the movement of the ovum in the uterus before it becomes permanently attached. Different conditions of the mucous membrane of the uterus have an influence upon the insertion of the ovum. Endometritis undoubtedly causes the death of many impregnated ova; while in other cases the ovum becomes attached to the lower portion of the uterus, which may be free from pathological lesions. Uterine myomas are often the indirect cause, through their accompanying endometritis, of placenta prævia. Above the internal os the placenta develops in the decidua capsularis, which forms the external envelope at its deepest portion, covering the os uteri, and becoming the lower portion of the placenta prævia. The nourishment of this portion of the placenta is obtained through the decidua, whose vessels obtain blood from the sinuses of the uterus. Adhesions between the capsular decidua and the decidua vera rarely occur at the opening of the Fallopian tubes, and also at the internal os. Should such union develop, it is easily separated by slight hemorrhage. The placenta does not firmly adhere at the internal os because of its development in the decidua. In the early months of gestation placenta prævia may give the symptoms of carcinoma of the body of the uterus. The low attachment of the ovum and placenta prævia frequently cause interruption of the pregnancy. Many spontaneous abortions arise from placenta prævia. The bleeding in these cases is caused by the separation of the capsular decidua from the decidua vera through dilatation of the os, which opens vessels in the capsular decidua which are in communication with the placental site. Later, partial separation of the placenta follows, or laceration of the placental tissue. The indications for treatment are to compress the bleeding vessels at the site of the placenta and dilate the cervix. In extreme cases total extirpation of the uterus by abdominal section may be indicated.

Induction of Labor with the Modified De Ribes Bag.—Brodhead (*Amer. Jour. Obstetrics*, May, 1912) reports 139 cases of induced labor, 75 being private patients and 64 hospital cases. The method of introducing the bag is as follows: The usual preparations having been made, a 1 per cent. lysol vaginal douche is given, and the cervix dilated with the finger and with a steel dilator sufficiently to permit the introduction of one of the bags. The bag is twisted, the base of the bag pulled out, and the bag rolled up and carefully passed by forceps into the cervix, either by inspection or vaginal touch, and slowly filled with a sterile solution of lysol or salt. For this purpose the writer has devised a glass syringe with a rubber plunger which can be readily sterilized. The ordinary Davidson syringe may be used. When the bag has been completely filled the stem is clamped and tied. As a rule no traction is made, unless dilatation must be rapid, when traction is made at intervals of ten or fifteen minutes. When the first bag is expelled through the cervix, if labor has not begun, a larger one is introduced. This is usually followed in a few hours by the beginning of active labor. Where the cervix is almost completely dilated

by the bags without setting up active pains, the membranes may be ruptured, and if necessary delivery completed by forceps or version. Bags No. 2 and 3 were used in 73 per cent. of cases. In 41 cases labor was induced for contracted pelvis; in 27 for toxemia; in 19 for a large child; in 15 for overdue pregnancy; in 13 because the patient was at term and anxious to get through; and in 11 for a previous history of uterine inertia with instrumental delivery; in 4 cases the menbranes had ruptured without labor developing; the other cases were induced for unusual conditions. In 6 cases, or 3 per cent., the membranes were accidentally ruptured during the insertion of the bags; in 3 cases, or 10 per cent., labor failed to develop with the use of the bags. In 85 per cent. of the primiparæ who were private patients, the introduction of not more than two bags was sufficient to bring on labor. In 2 patients where the bags failed to cause pains, they softened the cervix, and when the membranes were ruptured labor developed. In 42 multiparæ who were private patients, more than one-half were delivered by the use of one bag only; about one-third required the use of two. In 4 multiparæ, or 9 per cent., the bags failed to produce labor. In approximately 83 per cent. of multiparæ who were private patients, labor was induced by the use of not more than two bags. In cases where the bags failed to induce labor the patients were delivered by version or forceps, and in these cases the bags softened and dilated the cervix. An anesthetic was necessary for inserting the bags in one-sixth of the cases. In private primiparous patients labor began at once in 45 per cent., within twelve hours in 73 per cent., and within thirty hours in 79 per cent. With the private multiparæ, labor immediately began in 22 per cent., within twelve hours in 63 per cent., within thirty hours in 85 per cent. If both private and hospital primiparæ are considered, labor began at once in 49 per cent., within twelve hours in 76 per cent., within thirty hours in 85 per cent. With the multiparae, immediate labor followed in 31 per cent., within twelve hours in 68 per cent., within thirty hours in 89 per cent. If all cases together are considered, immediate labor followed in 37 per cent., within twelve hours in 70 per cent., within thirty hours in 88 per cent. In all the primiparous patients, on an average eight hours and twenty-two minutes elapsed before labor developed; in all multiparous patients, ten hours and twenty-two minutes. The average for all patients was nine hours and forty-one minutes. The length of the induced labor averaged in primiparæ twenty-two hours and nine minutes; in multiparæ fifteen hours and fifty-two minutes; or in all, eighteen hours and two minutes. In all these cases 49 per cent. had normal labor, 21 per cent. low forceps, 11 per cent. medium forceps, 3 per cent. high forceps, 10 per cent. version, 3 per cent. breech extraction, 1 per cent. craniotomy, 1 per cent. Cesarean section, and 1 per cent. died without delivery. Among the 139 cases the use of the bags changed the presentation in 7, or 5 per cent. In only one of these cases was the outcome of the labor changed because of the use of the bag. Presentation or prolapse of the cord occurred in 6, or 4.3 per cent. In one case the bag slipped above the head, but labor developed and proceeded normally, and the bag was readily removed. There was practically no morbidity among the private patients, and but trifling morbidity among the hospital patients. The patient who died undelivered perished from eclampsia.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

X-ray Treatment of Gynecological Skin Affections.—RUNGE (*Münch. med. Woch.*, 1912, lix, 1597) reports having treated 7 cases of severe idiopathic pruritis vulvæ with the *x*-rays, with complete success. There were no cases in which diabetes, or a leucorrheal discharge, was present. In 5 of the patients complete cessation of itching occurred after one to three treatments; 2 others required a few more treatments, but in these also a complete cure was eventually attained. Runge has had like favorable results in the treatment of 2 cases of severe eczema of the vulva due to an irritating vaginal discharge; the discharge was treated simultaneously by the usual methods, but Runge attributes the cure of the eczema to the *x*-rays, as the discharge had been treated for some time previous to beginning the use of the rays, with no apparent benefit to the skin condition. In 1 case of advanced kraurosis, practical disappearance of the itching was brought about by *x*-ray treatment, but no other effect could be observed. In the treatment of these conditions Runge uses a tube somewhat harder than those usually employed for dermatologic purposes. Since we do not know whether the seat of the trouble in pruritis and allied affections is purely superficial or somewhat deeper, he considers it advisable to use a tube which, in addition to the rays of superficial action, gives off some of a moderate degree of penetrating power. An exposure amounting to just short of an erythema-dose is given, either at one sitting, or divided between two successive days, and an interval of two to three weeks then allowed to elapse before the next treatment.

Constipation and Headache in Women.—In an article bearing the above title, REED (*Jour. Amer. Med. Assoc.*, 1912, lix, 354) expresses the belief that in many patients presenting the very common symptom-complex of constipation, headache, painful menstruation, tender ovaries, with more or less displacement of the uterus, the real source of the trouble lies in a displaced stomach and colon. Such patients are usually treated gynecologically solely on the assumption that the constipation may be due to the pressure of a retro-displaced uterus on the rectum, that the headaches are of reflex origin from the genital organs, and so forth. In many of these women, however, gynecological treatments or operative procedures produce no relief from the constant headaches; in such cases a careful *x*-ray will generally show a condition of gastrocoloptosis to be at the bottom of the trouble, and not until this is properly corrected do the symptoms, resulting largely from the absorption of toxins, disappear. While not for a moment denying the importance of correcting any marked displacements of the uterus

which may be present, nor assuming that every case in which some ptosis of the stomach and colon is present is necessarily accompanied by the above mentioned symptoms, Reed emphasizes that where such demonstrable lesions are present, associated with these symptoms, the gastro-intestinal condition will generally be found to be of far greater etiological importance than the gynecological.

Relative Value of Various Substances Used as Douches.—A systematic test of a number of the commoner substances used as ingredients of vaginal douches has been made by POLANO (*Zeitschr. f. Geb. u. Gyn.*, 1912, lxx, 394), in order to determine their relative effect on the chemical reaction and bacterial content of the vagina. For this purpose each substance has, as a rule, been tried on three dispensary patients, some of whom showed clinically symptoms of inflammation of the vagina, others of whom did not. The method of making the examination was briefly as follows: A tri-valve speculum was introduced and the valves spread apart. A platinum loopful of secretion was then taken from the right side of the vagina near the introitus, one from the left side, and one from each vaginal vault. From these, cover-slip smears were made, and examined microscopically. Four similar loopfuls were inoculated on agar plates and cultured. The speculum was then removed, and 1 liter of water containing the substance to be tested given as a douche to the still recumbent patient. This process was repeated in each case on three successive days. In many instances there was a marked lack of correspondence between the appearance of the smears and the cultures, the plates often showing almost complete absence of growth after treatment, while the smears apparently contained as many organisms as before. Polano believes the explanation of this to be that many of the organisms become temporarily reduced in virulence by the treatment, and while still being present, do not possess enough vitality to grow well. He has not found any permanent effect to be produced on the chemical reaction of the vagina, nor any change in the character of the bacterial flora to be brought about by any of the substances tested, though a quantitative diminution in the bacteria present could in many cases be demonstrated. The most effective substances in this respect were found to be alum, alcohol, alsol, silver nitrate, and bolus alba. Less satisfactory, but still of some value, were lysoform and iodine, while pyroligneous acid, lysol, and lactic acid gave the poorest results. It is evident, Polano concludes, that dessicating and astringent properties are of much greater importance in substances to be used as douches than bactericidal power or acidity.

Control of Hemorrhage in the Radical Operation for Carcinoma Uteri.—One of the most important factors in producing the very high primary mortality of the so-called "extended" or Wertheim operation for carcinoma of the cervix (averaging in most statistics about 20 per cent.) is conceded by most authors to be hemorrhage—not so much arterial bleeding, as venous oozing from the deep pelvic veins, which it is at times very difficult to control. PETERSON (*Surg., Gyn., and Obstet.*, 1912, xv, 135) has found this to occur chiefly in three places: (1) From the transverse vesical veins which run across the ureter,

(2) from the veins which lie close to the uterus and the ureter, and (3) from the veins posterior to the uterus lying in close connection with the rectum. In his experience hemorrhage from the last source is, as a rule, easily controlled; that from the vesical veins is best managed by separating the bladder from the vagina and uterus in the median line only, never trying to separate it at the sides until after the vesical veins have been secured by forceps on each side of the ureter. They may then be tied, cut, and the ureter dissected out of its bed without danger. Bleeding from the remaining veins can usually be controlled by pushing the ureter away from and down into the pelvis, clamping always toward the uterus. In this way danger of injuring the ureter is avoided. FROMME (*Zeitsch. f. Geb. u. Gyn.*, 1912, lxxi, 321), in discussing the same subject, says that he has seen 2 cases in which severe hemorrhage came from large venous sinuses situated in the dense connective tissue so closely attached to the pelvic wall that no ligature could be applied. Packing was ineffectual, and the only way to stop the bleeding was to catch the vessels with long, thin artery forceps. Since it was impossible to replace these by ligatures, they were left in position, the handles protruding through a small opening at one end of the abdominal incision. The forceps were allowed to remain in place for forty-eight hours; both patients had an uneventful convalescence, but one had to be subsequently re-operated upon for a small recurrence. The same difficulty was again encountered, and the same procedure carried out, with equal success.

Histology of Pyosalpinx.—A very decided opinion as to the impossibility of distinguishing histologically between salpingitis of gonorrheal origin and that due to other forms of infection has been recently expressed by MILLER (*Monatsschr. f. Geb. u. Gyn.*, 1912, xxxvi, 211). As is well known, Schridde and other authors have advanced the hypothesis that gonococci produce very definite and specific changes in the tube, which are not produced by other bacterial invaders, these changes consisting chiefly in a thickening of the mucous folds, with loss of surface epithelium, and the formation of adhesions between adjacent folds, but more especially in an infiltration of the folds by masses of plasma cells, lymphocytes, and lymphoblasts. The most important elements of all he considers to be the plasma cells, from the presence of which in any considerable numbers, in the tissue or in the free exudate, "a positive diagnosis of gonorrhea is justifiable." Miller, however, maintains that theoretically it is very difficult to understand why plasma cells should possess a specificity in the tube which they do not show in any other part of the body. They are found, as has been repeatedly shown by various authors, in many forms of inflammatory granulation tissue, in infectious granulomas, in the primary lesions of syphilis, and in the brain in various conditions, such as lues cerebri, dementia paralytica, acute alcohol and phosphorus poisoning, idiocy, sleeping sickness, etc. Miller does not rest his objection to Schridde's teaching on theoretical grounds alone, however. He has found in several cases of tuberculous pyosalpinx large numbers of plasma cells present, reaching to as high as 25 per cent. of the elements composing the free exudate in the lumen. In numerous cases of streptococcic tubal infection *post abortem*, in which there were no

grounds for suspecting the presence at any time of a gonorrheal infection, and in several of unilateral pyosalpinx following appendiceal abscess, in which gonorrhea could be positively excluded, he found plasma cells in large numbers, and all the other histological features considered by Schridde to be characteristic for gonorrhea. He concludes, therefore, that these criteria are all worthless, and that we do not possess at the present time any means of distinguishing with certainty between tubal infections due to the gonococcus and those due to the streptococcus or staphylococcus, except in the comparatively small group of cases in which it is possible by staining or cultural methods to demonstrate directly the invading organism.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASS.,

AND

ARTHUR I. KENDALL, PH.D., DR.P.H.,

DEPARTMENT OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL.

Infectious Abortion and its Relation to Man.—THEOBALD SMITH and MARSHALL FABYAN (*Centralbl. f. Bakt., Orig.*, 1912, lxi, 549 to 555), MARSHALL FABYAN (*Jour. Med. Research*, July, 1912, xxvi, 441 to 487) EDWIN S. GOOD (*Kentucky Agr. Exp. Sta. Bull.*, p. 165), FRANK M. SURFACE (*Annual Report of the Kentucky Agr. Exp. Sta.*, 1912, pp. 303 to 366) and others have recently studied a disease of cows and mares known as infectious abortion, which appears to threaten man. The disease is little known to students of human medicine, and a brief review of its essential features is therefore given. It has been suspected for nearly a century among farmers and breeders of horses and cattle that abortion was contagious in many instances and might spread from animal to animal in a heard. Not until 1895, however, was this suspicion made definite. In that year the Danish veterinarian, Professor Bang, and his assistant, Stribolt, isolated a small bacillus from abortive cows which has been proved beyond all doubt to be the cause of infectious abortion among cattle. Owing to certain peculiarities in the method of growth of this bacillus, many of the best pathologists have failed, however, to find it for a long time. Recently, however, a number of investigators in this country and abroad have isolated the organism and subjected it to careful study both culturally and experimentally. There can be but little doubt that this organism causes a very large economic loss yearly in this country and abroad. Statistics are not available for the most part, but Wall showed that among herds in Denmark, where infectious abortion was known to be present, more than 93 per cent. of the abortions were due to this specific organ-

ism. Among herds where slips occur only rarely, that is to say, in herds apparently not infected, he found that 27 per cent. of the abortions were in all probability due to this infectious disease. Similarly, Zwick, in Germany, has also called attention to the fact that this disease is far more widely spread there than is generally recognized.

Classification of Abortion in Live Stock.—Williams, writing on veterinary obstetrics, recognizes three distinct classes of abortion in domestic animals: (1) Sporadic or accidental abortion; (2) enzoötic abortion due to some infectious disease of the mother, such as tuberculosis, which brings about the death and expulsion of the fetus as a complication of the maternal disease; and (3) infectious abortion, an infection of the fetus and its membranes, which causes the death and expulsion of the fetus or its expiration in the living and febrile state at any period of gestation from the date of conception to the normal conclusion of pregnancy without directly introducing material evidence of disease in the mother.

Manner of Infection.—It was originally believed that infection was transmitted through the bull, but recent investigations seem to show very definitely that the main channels of infection are through the vagina and also through the alimentary canal by ingestion. These investigators believe that infection may reach the uterus even before pregnancy, setting up in the uterus an inflammatory process between the fetal and maternal membranes, resulting in a purulent exudate which causes a partial separation of these membranes and the premature delivery of the fetus. Investigations also indicate that the organism is able at times to actually enter the circulation of the fetus through the medium of the placenta to the blood stream.

Symptoms.—McFadyean and Stockman, of the English Abortion Committee, found that animals experimentally infected with the disease occasionally exhibit a slight rise in temperature after infectious material was given. This is not always the case, however, and they decided that "under natural conditions infection is insidious and usually no noticeable symptoms arise until the animal is about to abort."

The Morphology and Cultural Characters of B. Abortus.—The organism is from 0.5 to 0.6 microns in diameter and from 0.6 to 3 microns long. There may be some variation in the length. The diameter is fairly constant. The organisms ordinarily lie separately or in pairs, very rarely in chains. There is no motility although Brownian movement may be very pronounced. The bacillus stains readily with all ordinary dyes, staining uniformly, as a rule, although occasionally certain irregularities in staining may be noticed. The organism is Gram negative; no capsules, flagella or spores have been demonstrated. In old cultures, degenerated and involution forms may be seen and rarely branched forms. On agar colonies appear as rather small transparent growths resembling dewdrops. Later they assume a yellowish-brown color. Growth on gelatin is very slow, probably because of the low temperature (20°) at which gelatin is incubated. After a week or ten days, however, small colorless colonies usually appear. No liquefaction of gelatin takes place. On the agar-gelatin serum medium of Bang a growth occurs either at the surface or in a zone sharply circumscribed and immediately below the surface.

In ordinary broth a slight clouding usually appears after forty-eight hours, which gradually becomes rather dense, and then after a variable period tends to clear up. As a rule, no pellicle forms on the surface even after long incubation. The organism grows fairly readily in milk without, however, producing any acid. In fact a slight but definite amount of alkali is produced in this medium. The optimum temperature for growth is 37° C. The organism grows very slowly at 20° C. According to Preisz, the organism withstands exposure to 50° C. for thirty minutes, but is killed at 55° C. usually within ten minutes.

THE DIAGNOSIS.—MCFADYEAN and STOCKMAN have attempted to diagnosticate infectious abortion by means of a substance which they call "abortin." This substance is prepared in precisely the same manner as is mallein. The results although interesting are not wholly satisfactory. A much more satisfactory procedure appears to be the well known deviation of complement method which is carried out in the usual manner. Fabyan has studied the pathogenesis of B. abortus in guinea-pigs and finds that although the disease in cows is apparently a rather strictly limited one, in guinea-pigs the organism produces a marked general infection. Generally speaking the most characteristic feature of the guinea-pig disease is a greatly enlarged spleen showing large edematous areas of degeneration and a swollen liver with numerous necrotic areas. Similarly Schoreder has studied the same disease and has noted the same general phenomena at autopsy, and has called attention to the fact that the lesions may resemble, in a general way, those of tuberculosis. He has made an interesting observation that in the males very frequently there is a more or less complete breaking down of the testicles. In rare instances there may be paralysis and a peculiar type of joint disease. It is a very significant fact that in a few instances women who give a history of abortion show, by the deviation of complement method, the presence of B. abortus. Realizing that this organism may occur, and apparently does occur in milk, the significance of these discoveries cannot be overlooked. Fortunately heating milk to the temperature of 60° C. for a few minutes will certainly remove this danger. From the hygienic point of view this disease which hitherto has not received the attention which it deserves, is an entity which must be taken into consideration not only with respect to the dairy industry, but also must be regarded as a probable invader of man.

Alimentary Anaphylaxis.—O. H. RICHET (*Compt. Rend. Soc. Biol.*, 1911, i, 44) has thrown additional light upon the interesting occurrence of acute symptoms caused by various substances such as shellfish, strawberries, and sometimes by standard articles of diet such as eggs, veal, oatmeal, etc. In the light of our present knowledge it appears that these disturbances are instances of local hyper-susceptibility, and that the acute poisoning is brought about by the sharp muscular and vascular reactions which take place in the sensitized intestinal mucosa upon ingestion of the particular substance in question. Richet gave 0.37 gram per kilo of krepitin to a dog by the mouth, and four weeks later 0.14 gram per kilo also by the mouth. This produced mild indications of anaphylaxis. Two days later the dog was refractory to an intravenous injection while a control dog similarly treated, but

which did not have the second feeding by the mouth, promptly died in anaphylactic shock. Richet also found that when krepitin is given by the mouth the sensitized animals showed a marked leukocytosis at the second feeding. If the animal survived the anaphylactic shock the late symptoms of poisoning due to the krepitins did not appear, therefore they were rendered immune.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.,

LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL; SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL VICTORIA HOSPITAL, MONTREAL.

The Influence of Local Anemia upon the Action of Poisons and upon Infective Processes.—R. BESTELMEYER (*Br. Beitr.*, 1912, Band lxxviii, Heft 2, S. 333) notes, as a result of his experiments, some interesting facts. Although there is no actual killing of virulent baccili by reason of a locally produced anemia, yet the resorption of injected soluble poisons is so retarded that ordinarily fatal doses may be injected without producing a fatal effect. This was proved by the use of various snake poisons. With the slowing of the capillary current there is a corresponding lowering of the rate of absorption; with a quickened capillary current more poison is absorbed. In infective states, local anemia delays the entrance to the blood stream of bacteria and their toxins. The general and local manifestations appear later, but there is a greater tendency to localized necrosis, although secondary abscesses by way of the lymphatics are less prone to occur. Passive hyperemia, Bestelmeyer points out, is anemia, as far as the arterial blood is concerned.

Vaccination with Sensitized Agents.—BESREDKA (*Bull. d. l'Inst. Pasteur*, June 30, tome x, No. 12) deals anew with the question of vaccination by means of agents, living or dead, that have been attenuated in various ways. In the case of tubercle bacilli, if attenuated, sensitized bacilli are used, they are not only themselves absorbed more quickly than ordinary bacilli, but they in some way hasten the absorption of bacilli injected subsequently to their own entry into the body. The sensitized bacilli (if one may so translate *sensibilisés*) are better borne by the animal than are the non-sensitized, to the extent that with the former, repeated injections do not kill; as to the power as a vaccine, guinea-pigs treated with sensitized bacteria contracted disease from subsequent inoculation with ordinary virus, but after long delay and of light grade of severity. Meyer used the sensitized vaccine on 47 persons; localized tuberculosis, such as abscess or fistula, healed rapidly, while bone and joint lesions were quickly bettered; 40 out of 47 cases showed definite amelioration. Vallée and Guinardre report equally good results in 30 women; all these observers unite in declaring

the innocuousness of the sensitized bacteria. With reference to sensitized pneumococci as a vaccine, Leon and Aoki have had good results in experimental animals; the innocuity is quickly obtained and is more durable than in the case of ordinary pneumococci. A negative phase is not obtained after injection, and the immunity to subsequent inoculation was sometimes very striking. Vaccination against typhoid fever is of interest in view of the fact that Besredka (with Metchnikoff) has used the living sensitized typhoid bacilli for the purpose. Encouraged by the results obtained in chimpanzees, they have carried on the experiments in man. Alcock has proved in the case of 44 persons that the procedure is a harmless one; the sensitized vaccine leads to little or no general or local reaction, and Besredka states that 700 human subjects of recent experiments bear witness to its harmlessness. He cites the work of Garbat and Meyer, as to the effect on the serum of the inoculated animals. The immunity of these animals surpassed that of the animals immunized in the old way, nevertheless, neither agglutination nor fixation of the alexin could be cited as indications of this immunity.

Some Facts about the Epidemiology of Tuberculosis.—A. CALMETTE (*Ann. de l'Inst. Pasteur*, July, 1912, vol. xxvi) has brought forward considerable evidence upon the existence of tuberculosis in the French colonies. In the tropics, tuberculosis goes hand in hand with civilization. Black races, where they are uncontaminated from without, remain very free from the disease. None, however, of the races studied were immune, and the last comers to civilization were less immune than those who had mixed somewhat with the outside world. "It is no longer possible," says Calmette, "to support the hypothesis formulated by von Behring in 1903 that pulmonary tuberculosis in the adult is only a late manifestation of an infection of bovine origin, contracted in the earliest months of life as a result of the ingestion of milk from a bacilli-carrying cow." Among the indigenous population of West Africa and Indo-China, infants are found free of infection up to the time of weaning, after which they are subject to familial and other infections, especially by the custom prevailing in Indo-China, by which some older person chews the rice before putting it into the child's mouth. Later, the pipe, the betel, or the kola nut is freely transferred from mouth to mouth. In West Africa, Indo-China, the Antilles, and in Oceania, "interhuman" contamination alone is at work, since children drink no cow's milk, and indigenous cattle are as yet uninfected. In older colonies, the conditions approximate to the state of affairs seen in Europe, and tuberculous milk must be admitted to be in some degree responsible.

The Process of Vital Staining.—W. SCHULEMANN (*Zeitsch. f. exper. Path. u. Ther.*, 1912, Band xi, Heft. 2) makes certain observations upon the relationship between the chemical constitution of cells and their stainability during life. He considers that the granules in the cells that exhibit the stain are formed as a result of the entry of the coloring material to the cell, and that there occurs a chemical combination between the coloring matter and a (hypothetical) reaction-body which is formed for the purpose. This view is supported by the fact that in intensifying experiments where the color is re-administered, the

number of granules increases but not the intensity of color of the individual granule. The form of these granules is not constant, and seems to depend upon the speed of diffusion of the coloring agent, being smaller and more uniform with slowly diffusing agents, larger, more irregular, and even at times cubical with those agents that diffuse rapidly. Attempts at combined staining of the granules are unsuccessful, and the granules are entirely absent in certain types of cell, both of which facts are cited in favor of the existence of reaction-bodies; even stronger evidence is the observation that in a cell where poisons are present which damage the reaction-bodies, these become free and diffuse out of the cell. Goldmann considers the reaction-body to be a lightly-bound fat-albumin molecule or group of molecules.

A Comparative Study of Antibodies.—It is daily becoming better understood that all antibodies that are produced by the cell are not available for the cure or prevention of infection or disease; that the existence of one antibody in excess does not speak for the necessary existence of another. KOLMER (*Jour. of Med. Research*, July, 1912, vol. xxvi, No. 3) found, in typhoid and cholera immune serums, that there is no relation between the degree of complement fixation and the opsonins, agglutinins, and bacteriolysins, while there did appear to be a relation between the amount of opsonins and of bacteriolysins. The same antigen may stimulate the production of different antibodies, lysins, agglutinins, opsonins, antitoxins, and other complement-fixing bodies, and one antigen tends to produce excess of one or more antibodies, while another antigen produces others. Each antibody has a direct relationship to its antigen, but not necessarily to the other antibodies. Nevertheless, the existence of an excess of one or more of the antibodies is often good presumptive evidence of the existence of excess of yet others. The presence of complement fixation is not, however, such good evidence as it at first appeared, of the existence of protective antibodies. Kolmer found that the complement-fixing body (an antibody in one sense of the word) bore no relation to the other antibodies. In curative and prophylactic serums, it is true that the antitoxins, the bacteriolysins, and the opsonins bear some relation quantitively one to another; but the agglutinins (and precipitins) are not directly opposed to the antigen, and are not definitely protective to the organism, although the serum which shows an excess of these probably contains excess of the other bodies which *are* protective. Complement fixation power, Kolmer concludes, is not a measure of bactericidal power; there is probably a special antibody produced which is capable of binding hemolytic complement without, at the same time, being protective to its own organism or destructive to the antigen which gave rise to its production.

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All communications should be addressed to—

DR. GEORGE MORRIS PIERSOL, 1927 Chestnut St., Phila., Pa., U. S. A.